The Timeline of Post Exertional Malaise in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

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ABSTRACT

PURPOSE: To investigate the timeline of post-exertional malaise (PEM) using objective and subjective measures in Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). The primary aim was to determine whether PEM extends beyond 24-hours, and if a 48-hour or 72-hour repeated exercise protocol would provide additional information as a diagnostic tool. The secondary aim was to analyse subjective patterns of fatigue during PEM.

METHODS: Sixteen ME/CFS and 16 age and gender matched controls participated in the study. Participants were randomly assigned to either a 48-hour or 72-hour repeated cardiopulmonary exercise test protocol on a cycle ergometer. Objective measures were recorded at anaerobic threshold (AT), respiratory exchange ratio (RER) and maximal exercise. All ME/CFS participants recorded their subjective fatigue 7-days prior to and 10-days post exercise utilising the daily diary of fatigue.

RESULTS: Results from the 48-hour and 72-hour protocol indicated no decline in functional capacity in any group across days. There was a significant increase in workload and $\%VO_{2max}$ at AT within the 72-hour ME/CFS group only. Subjective timelines of fatigue showed significant differences between the 48-hour and 72-hour protocol, with the 48-hour ME/CFS group taking significantly longer to recover (mean 11 days) than the 72-hour ME/CFS group (mean 5 days). Conversely, both control groups were recovered in less than a day. However, there was high variation across measures of subjective fatigue among ME/CFS participants.

CONCLUSIONS: The results of this study further support the use of 24-hour repeated protocols to determine functional decline during PEM. Results also provide new information regarding a potential improvement in function 72-hours after an initial exercise bout in ME/CFS. Subjective results indicate no identifiable pattern in relation to subjective fatigue during PEM. Future research should focus on a larger clinical trial to further understand the implications and consistency of the data from this study.

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LIST OF ABBREVIATIONS

A

AT	Anaerobic threshold

B

BMI	Body mass index
bpm	Beats per minute
BP	Blood pressure

C

CBT	Cognitive behavioural therapy
cm	Centimetres
CO_2	Carbon Dioxide
CFS	Chronic Fatigue Syndrome
CCC	Canadian consensus criteria
CTRL	Controls

G

GET	Graded exercise therapy

H

HR	Heart rate
HR_{max}	Heart rate max

I

ICC	International consensus criteria

K

Kg	Kilograms

M

m	Metres
ME	Myalgic Encephalomyelitis
$ml.kg.min^{-1}$	Millilitres per kilogram per minute
MS	Multiple Sclerosis
mmHg	Millimetres of mercury

P

PEM	Post-exertional malaise

R

RER	Respiratory exchange ratio
RPM	Revolutions per minute
RPE	Rating of perceived exertion

S

SD	Standard deviation

V

V_E	Minute ventilation
VO_2	Oxygen consumption
VO_{2max}	Maximal oxygen uptake
VT	Ventilatory Threshold

W

W	Watts

CHAPTER ONE: INTRODUCTION

Myalgic Encephalomyelitis (ME) initially appeared as the name for this illness in the 1950's and was defined in detail soon after, by Price (1961). The condition was later termed Chronic Fatigue Syndrome (CFS) and defined further by Holmes et al., (1988). Today, "ME/CFS" is commonly used in discussion. It is a debilitating condition resulting in severe fatigue and a range of other symptoms including: sleep disturbance, pain, bowel irritation, frequent infections and cognitive impairment (Yancey & Thomas, 2012). Since 1988, research within the field has focused on identifying it's aetiology, diagnosis and recently, potential treatment methods (Jason et al., 2012). It is evident from its aetiology that numerous processes play a role in the development of CFS. It is proposed that the condition may occur as a result of a stressful life event (physical or emotional) and an inability to recover from this event (Moss-Morris et al., 2013). Immune abnormalities, muscular dysfunction and faulty energy processes are all factors that play an intertwining role in the pathology of the condition and research is on-going to better understand these various pathologies (IOM, 2015).

Currently, the method of diagnosis for ME/CFS involves a subjective symptom-based questionnaire where answers are matched against a set of criteria (Haney et al., 2015). The criteria are based on clinical consensus information, whereby evidence is gathered and collated from a range of questions regarding the symptoms commonly experienced by those with ME/CFS (Yancey & Thomas, 2012). To-date there is a lack of statistical and scientific validation and therefore no criteria has been considered the "gold-standard" for ME/CFS diagnosis (Twisk, 2014). Of the criteria developed three have been recommended and utilised in research and clinical contexts, these include: the Fukuda Criteria (1994), the Canadian Consensus Criteria (2003) and the International Consensus Criteria (2011) (Sunnquist et al., 2017). Each has their strengths and weaknesses and although it is argued that none are ideal, they are still a useful tool for on-going research (Twisk, 2014).

Beyond subjective diagnostic criteria, objective markers have been identified as playing a crucial role in the journey to find a physiological biomarker within this population (Twisk, 2014). In recent years, studies on immunity, muscular systems and energy pathways have investigated potential biomarkers for this condition (Gonthier & Favrat, 2015). An important area for further explanation is the function of exercise protocols as a diagnostic tool. Post-exertional malaise (PEM) is described as the exacerbation of many core symptoms following exertion. It has been termed a "hallmark" symptom of CFS. Post-exertional malaise is not evident in other conditions where fatigue is also experienced and for this reason, many are suggesting that if this symptom could be captured objectively via exercise testing, it may provide a unique point of reference for diagnostic assessment (Hodges et al., 2017). To-date, single exercise protocols and 24-hour repeated exercise protocols have been primarily investigated. Single tests are noted to bypass crucial information regarding what occurs in the time following an initial exercise test (Hodges et al., 2017). It has become apparent that differences in functional capacity are only evident following the first test, therefore to truly capture the nature of PEM a repeated protocol is required. In those with CFS, repeated exercise protocols are providing experimental evidence for a decline in function during PEM 24-hours post exercise (Hodges, Nielsen, & Baken, 2017; VanNess, Snell, & Stevens, 2007).

Although, this area of research is in its infancy and questions still remain regarding the timeline of PEM. Subjective studies investigating PEM suggest that it may extend beyond 24-hours and even worsen further at 48-72 hours post-exercise. Exercise protocols extending past 24-hours may better highlight PEM objectively (Yoshiuchi et al., 2007). Before exercise protocols can be advocated as a diagnostic tool for CFS, it is important to determine details regarding what type of protocol will have the best accuracy (Hodges, Nielsen & Baken, 2017). If PEM does worsen beyond 24-hours, 24-hour repeated protocols may under-diagnose those whom experience a later onset of PEM, consequently there is a need to define this timeline.

This thesis begins with an extensive contemporary literature review (chapter two) that provides background information to CFS. It will investigate current diagnostic tools used for the assessment of ME/CFS patients, assess the advantages and disadvantages

of current tools, investigate the purpose of exercise as a diagnostic tool and evaluate the timing of PEM and how this may assist in guiding treatment options within ME/CFS. Following the literature review, specific aims and objectives will be outlined (chapter three) as well as the methods of the current study (chapter four). The results will be presented (chapter five) and then discussed alongside limitations and recommendations for future research (chapter six), and the thesis will end with conclusions (chapter seven).

CHAPTER TWO: LITERATURE REVIEW

2.1 ME/CFS Background

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a condition characterised by severe, persistent fatigue lasting longer than 6 months and a number of other debilitating symptoms, which cannot be explained by any other medical condition (Amihaesei & Cojocaru, 2014; Gonthier & Favrat, 2015). Some of the earliest research surrounding ME/CFS as a recognised medical condition arose when Price (1961) and Holmes et al., (1988) defined ME/CFS and some of the prominent symptoms experienced (Jason et al., 2012). The symptoms now commonly associated with the condition include: muscle and joint pain, sleep disturbance, bowel irritation, frequent infection, cognitive impairments and anxiety, amongst many others (Amihaesei & Cojocaru, 2014). Due to the numerous symptoms, ME/CFS has profound implications in regards to quality of life for those living with the condition (Tanaka & Watanabe, 2010). Daily functioning for those with ME/CFS is greatly reduced and consequently, approximately 50% of sufferers are forced to leave their job once diagnosed, resulting in financial insecurity; with a full recovery rate of only 5%, implications are likely to be long-lasting (Amihaesei & Cojocaru, 2014).

The prevalence of ME/CFS is extremely difficult to determine due to complications surrounding diagnosis (Johnston, Brenu, Staines, & Marshall-Gradisnik, 2013). However, early literature indicated that in the United States alone, half a million people suffer from ME/CFS (Friedberg & Jason, 1998). More recently, a systematic review identified that prevalence ranges from 0.01%-4.8% depending on the diagnosis method used (Johnston et al., 2013). In 2015, a combination of studies estimated that between 0.3% and 0.9% of the population worldwide are currently diagnosed with ME/CFS (Gonthier & Favrat, 2015). In New Zealand an estimated 16,000-20,000 individuals with ME/CFS has been reported (ANZMES, 2017). To put this in perspective with other fatigue-related conditions, this is significantly higher than the prevalence of multiple sclerosis (~3000) but not as high as the prevalence of fibromyalgia (~1.3%/50,000) (ANZMES, 2017; Taylor et al., 2007; Theadom et al., 2011). It is also important to note that ME/CFS prevalence is higher in females than in males, with a ratio of approximately 1:4 (Faroa et al., 2015).

To-date, many studies have investigated the pathology of ME/CFS, with results suggesting a diverse and at times controversial range of possibilities as to why and how it develops (Gonthier & Favrat, 2015). Some of the earlier literature published by Friedberg and Jason (1998), outlined four potential contributing factors to ME/CFS; periods of high stress (physical and/or emotional), personality type in relation to how people deal with anxiety (and associated hormones), biological factors (such as how the brain adapts to infection) and the physical presentation of psychological stressors, known as somatisation. Moss-Morris, Deary and Castell (2013), propose a model that states that ME/CFS is a result of stressful life events occurring in vulnerable individuals. It has also been identified that many individuals diagnosed with ME/CFS also have a history of serious infections (Horowitz, 2015).

With investigations researching more specific physiological pathways including immune dysfunction, oxidative stress and mitochondrial dysfunction as potential causes for ME/CFS, objective research is building in this area (Gonthier & Favrat, 2015). The immune system appears to perform a significant role in fatigue-related processes with many studies providing evidence of altered immune cell presence and other immune abnormalities in those with ME/CFS (Bradley et al., 2013; Loebel et al., 2014; Stringer et al., 2013). The immune system may play a crucial role in the development of the condition (Bradley et al., 2013) but further research is required to understand this better. Not only are immune dysfunctions appearing within this group, but notable mitochondrial dysfunctions are also becoming apparent. Tomas et al., (2017) have identified that during a mitochondrial stress test, ME/CFS patients have abnormal energy transduction (especially under load) in comparison to healthy controls. It is thought that this may be due to the inability of this cohort to increase respiration in relation to increases in energy demands, which may result in the onset of premature fatigue (Tomas et al., 2017). As the immunological and physiological research continues, authors question whether these abnormalities are a part of the cause of ME/CFS, or simply an effect of the condition and therefore additional research is required to define these pathways.

In contrast to immunological and physiological findings, other research has emerged to suggest that ME/CFS is more related to psychiatric abnormalities and personality

disorders. It is suggested that psychological processes are more prominent as opposed to physiological pathways in the development of the condition (Tanaka & Watanabe, 2010), however it is not conclusive. This opinion was popular amongst early research in particular, leading many to doubt the legitimacy of ME/CFS as a "medical" condition (Horowitz, 2015). Many theories have speculated that various personality types respond differently to high-stress periods and that deficient coping mechanisms may lead to the development of ME/CFS; therefore, the adoption of differing behavioural strategies may be a useful treatment strategy (Tanaka & Watanabe, 2010). A recent study reported high incidence of obsessive-compulsive disorders and avoidant disorders within an ME/CFS cohort (Calvo et al., 2017). It is suggested that these types of disorders may contribute to a personality-based pathology in ME/CFS.

Aside from physiological or psychological processes causing ME/CFS independently, it has been proposed that the condition may result from a combination of these. Psychiatric processes (like obsessive compulsive disorder) are likely to have an effect on physiological processes such as the immune response, hence aspects from both may contribute to the condition and furthermore to the low incidence of recovery (Horowitz, 2015). The causation and pathology of ME/CFS is still being hotly debated. Although research is making progress, it is still poorly understood and thereby methods of diagnosis and treatment remain questionable.

2.2 Current Methods of Diagnosis

The diagnosis of ME/CFS involves excluding the presence of other underlying conditions using a subjective, symptom based questionnaire (Haney et al., 2015; Yancey & Thomas, 2012). Current diagnosis is based on clinical criteria that distinguishes ME/CFS from alternative medical conditions, which may have some symptom cross-over (Vallings, 2012). Since the evolution of ME/CFS as an isolated medical condition, experts have developed diagnostic criteria based on the majority of symptoms experienced by those with CFS, through the utilisation of clinical consensus material (Jason et al., 2015). Since the first criteria published in 1988, there are now a number of published criteria available for ME/CFS diagnosis. However, none of which have been deemed the "gold-standard" (Haney et al., 2015). Research appears to be divided as to which clinical criteria is most

accurate and whether they provide an accurate diagnostic tool (Morris & Maes, 2013; Rollnik, 2017). Variations across diagnostic tools make it difficult to diagnose within research and clinical settings and this lack of consistency causes many problems for those with ME/CFS in relation to being taken seriously by medical practitioners and by peers (Snell et al., 2013).

In total, there are approximately 20 proposed sets of criteria for ME/CFS diagnosis; eight of which are most utilised (Bruberg et al., 2014). These eight criteria are: The Holmes definition (1988), The Oxford criteria (1991), The London criteria (1994), The Fukuda definition (1994), the Canadian Consensus Criteria (2003), The NICE guidelines (2007), the revised Canadian Consensus Criteria (2010) and the International Consensus criteria (2011). Many of which have been revised and republished since their initial development (Brurberg et al., 2014). The aforementioned criteria have been assessed for accuracy, with three receiving preference for use, which will form the focus of this review; The Fukuda definition, the Canadian Consensus Criteria (CCC) and the International Consensus Criteria (ICC) (Jason et al., 2014).

The Fukuda criteria was one of the earliest developed (1994) and is frequently used in clinical and research settings; it involves three primary criteria. Individuals must have experienced more than 6 months of fatigue, a significant reduction in daily function/activity (of 50% or more) and currently experience four out of eight "core" symptoms from the following list – impaired memory or concentration, sore throat, tender lymph nodes, muscle pain, joint pain, headaches, un-refreshing sleep and/or post-exertional malaise (Brurberg et al., 2014; IOM, 2015).

The Canadian Consensus Criteria was later developed (2003) and involves a more detailed set of symptoms. Individuals must experience five "core" symptoms, two or more cognitive manifestations and at least one symptom from two of three other categories; autonomic, neuroendocrine and immune manifestations (Asprusten et al., 2015).

The third and most recent set of criteria is the International Consensus Criteria; developed in 2011 this criteria mitigates many of the observed flaws in other criteria and approaches the condition as one that influences a number of body systems (Johnston et

al., 2013). It involves mandatory post-exertional malaise (PEM) with at least one symptom from several specific symptom categories including: neurocognitive impairments, immune and gastrointestinal impairments and energy production/transportation impairments. Furthermore, it includes an altered criteria for youth exclusively, no longer requiring that fatigue has been present for 6 months or more prior to diagnosis (Johnston et al., 2013). Accurate diagnostic criteria is important in relation to effective treatment, but also to ensure the validity of ongoing research and because of its importance, investigations are continually looking to compare and improve criteria (Jason et al., 2015).

Although the Fukuda criteria is widely used, many studies have found it to be the least reliable of the three, due to its focus on psychopathology and out-dated symptom requirements (Jason et al., 2013; Jason et al., 2014). The criticism surrounding the Fukuda case-definition suggests that the criteria are over-sensitive in regards to psychopathology with a large focus on mental symptoms. Further criticisms indicate that it is likely to result in an overlap of symptoms for those who have underlying depression and/or anxiety type disorders (Brurberg et al., 2014). Furthermore, in comparison to the alternate criteria, the Fukuda allows for now termed "core" symptoms, such as post-exertional malaise, to be excluded in diagnosis. Patients are only required to have four of eight general symptoms; thus potentially leading to over diagnosis of those who don't experience one or more core symptoms, like PEM (Jason et al., 2014).

The symptom domains most effective in distinguishing between ME/CFS patients and healthy controls were investigated by Jason et al., (2014). The investigation found that post-exertional exhaustion and energy transport based symptoms provided for the majority of differences between groups, in comparison to psychopathology based symptoms. In conjunction with this finding, the Fukuda criteria is the least accurate in distinguishing between healthy controls and ME/CFS participants (76.2% accuracy) as it does not prioritise these domains compared to the Canadian Consensus Criteria (93.3% accuracy) and ICC (86.7% accuracy). These findings suggest that the Fukuda criteria has the least specific symptom make-up and is least likely to distinguish between groups, which further highlights the presence of out-dated symptom requirements within this definition (Jason et al., 2014).

The validity of the Canadian Consensus Criteria (CCC) has also been questioned on many occasions with research suggesting that the CCC may be too specific, leading to under diagnoses (Asprusten et al., 2015). Jason et al. (2013) compared groups of CCC with Fukuda and found that significantly fewer patients were categorised as having ME/CFS by the CCC and those who were, had severe, not moderate, symptoms. Asprusten et al. (2015) investigated the CCC in isolation across 120 adolescent patients, medically diagnosed with ME/CFS. They found that only 46 clinically diagnosed participants met the criteria, however it was observed that differences between those who did and those who did not, were marginal and overly discrete (Asprusten et al., 2015). It has been suggested that the CCC identifies a more impaired group of patients and may under diagnose in regards to those who experience some mild symptoms (Asprusten et al., 2015; Jason et al., 2015).

In order to overcome problems surrounding research validity, some researchers propose that more stringent criteria should be utilised in research settings to maintain validity. Alternatively, those participants who only meet less strict criteria (such as the Fukuda) separated from those who meet strict criteria to ensure that research participants have the same underlying medical condition (Jason et al., 2015). This would provide greater validity in regards to discussion and comparison across studies.

The ICC was developed with the intention of bridging the gap between weak and stringent criteria (Johnston et al., 2013). The CCC was utilised as a starting point, however a number of changes were made; for instance, at-least 6-months of fatigue was no longer a requirement (Carruthers et al., 2011). Experts involved in the development of the ICC state that the detailed symptom requirements are more selective, providing a suitable participant enrolment tool for researchers around the world (Carruthers et al., 2011). Some scholars recommend that a symptom based questionnaire along with a diagnosis from a medical practitioner would further validate the recruitment of ME/CFS patients for research purposes (Jason et al., 2009). In 2010, Leonard Jason developed an all-encompassing questionnaire called the DePaul Symptom Questionnaire which includes the requirements of other criteria as well as further details of symptom severity and frequency (Newton, 2017). It also asks ME/CFS patients whether they have a diagnosis from a doctor, or have been self-diagnosed (Newton, 2017). This questionnaire is highly

validated and has become a popular tool for researchers when recruiting ME/CFS participants (Jason et al., 2015).

Many researchers are now emphasising the importance of an objective method of diagnosis (Rollnik, 2017; Twisk, 2014). A recent literature review critically analysed diagnostic research on ME/CFS and concluded that inconsistencies exist across methods and there is inadequate evidence to warrant ME/CFS as a unique or independent condition (Rollnik, 2017). The importance of sound statistical validation, which currently does not exist, is also emphasised in a review by Morris and Maes (2013). Authors insist that ongoing research surrounding consensus-based criteria is unwarranted because subjective criteria do not pass external validation in the first place. A focus on physiological measures such as neuro-immune biomarkers would be more constructive. Although subjective criteria is not ideal, it is a mandatory step in effectively working towards a biological marker (Jason et al., 2015). Twisk (2014), also supports this stance, suggesting that well-defined criteria are crucial to diagnose ME/CFS. Moving forward, objective measures are needed to cement ME/CFS as a serious condition and to diffuse the debate surrounding its diagnosis.

2.3 Post Exertional Malaise (PEM)

Post-exertional malaise is the exacerbation of various core symptoms, such as: fatigue, sleep disturbance, cognitive deficits, headaches and muscle aches, following physical exertion of all intensities (i.e. daily tasks such as showering) (Jason et al., 2015). Research suggests that PEM usually lasts at least 24-hours, with some subjective studies suggesting it may extend up to two weeks (Davenport et al., 2011; Van Oosterwijck et al., 2010). Post-exertional malaise (PEM) is a definitive symptom of ME/CFS that has gained verification (Jason et al., 2015). Post-exertional malaise is described consistently as the most debilitating aspect of ME/CFS and is present in 95% of patients (Cook et al., 2017; Van Oosterwijck et al., 2010). In contrast, within the general population physical activity has been shown to increase energy levels, both acutely and chronically (Loy, O'Connor, & Dishman, 2013). Post-exertional malaise is important as it differs to what is experienced by healthy populations and it appears to be unique to ME/CFS as a medical condition i.e., it is not experienced in other conditions, including those that are also fatigue related, such

as depression, fibromyalgia and multiple sclerosis (Hodges et al., 2017; Van Oosterwijck et al., 2010).

Research across sports science and health fields supports the use of exercise as a means to both prevent and treat a wide range of health conditions (Penedo & Dahn, 2005). Exercise and cardiovascular disease has been studied extensively; exercise having profound effects on reducing its likelihood, serious risk factors and mortality rates (Sundquist, Qvist, Sundquist, & Johansson, 2004; Xiao, 2017). Exercise has also been shown to improve glycaemic control, improve functional capacity and reduce the likelihood of other diabetic symptoms occurring in diabetics (Balteanu, 2016; Burr & Nagi, 1999). Beyond the physical benefits, research also supports the use of exercise for psychological means with an improvement in quality of life for those living with various diseases, including Parkinson's, Alzheimer's, Cancer and Multiple Sclerosis (MS) (Bizière & Kurth, 1996; Fernandez et al., 2015; Mendiola-Precoma, Berumen, Padilla, & Garcia-Alcocer, 2016).

Exercise prescription has been widely researched within a number of fatigue related conditions. Exercise has been found to exhibit significant positive effects on fatigue levels in individuals with multiple sclerosis (Andreasen, Stenager and Dalgas, 2011), as well as individuals with fibromyalgia (Ericsson et al., 2016). In particular, it was identified that individuals with fibromyalgia who completed exercise, experienced an improvement in sleep quality, which in turn improved fatigue. Exercise has also been identified to display favourable effects on cancer survivors (post-chemotherapy), where a reduction in fatigue was observed alongside exercise interventions, including both resistance training and aerobic training interventions (Dennett et al., 2016). The positive influence of exercise on the health and quality of life in other compromised populations seems obvious, further highlighting the significance of PEM as a unique symptom for ME/CFS sufferers, whom commonly adopt exercise-avoidance behaviours due to PEM.

To-date, research investigating PEM has involved subjective measures of fatigue. In light of this, recent research is now investigating objective measures to assess PEM and better understand why exercise negatively affects those with ME/CFS (Jason et al., 2015; Staud, Mokthech, Price, & Robinson, 2015). Objective studies investigating PEM have used

exercise protocols (incremental or steady-state) with measures during and following exercise to assess both the immediate and delayed effects that exertion elicits (Hodges et al., 2017). These include subjective (questionnaires) and objective measures, involving physiological measures of functional capacity such as VO_{2max} and achievable workload (Keller, Pryor, & Giloteaux, 2014).

Some of the earliest research involving structured exercise to observe PEM was conducted by Sistio et al., (1998). This study involved a strenuous incremental treadmill protocol until volitional fatigue (or age-predicted HR_{max}) and subjective measures of fatigue for 7-days post exercise (Sisto et al., 1998). The ME/CFS group experienced a 10% decrease in daily activity following the test, accompanied by a 26.5% increase in rest needed throughout the day. These affects were evident up to 7-days post-exercise and were paradoxical to the response of healthy controls. This study only "encouraged" participants to reach age-predicted HR_{max} during the exercise test, therefore it is difficult to determine whether this test was maximal by current standards (Sisto et al., 1998; ACSM, 2012).

Subjective levels of pain during PEM was investigated more recently (Van Oosterwijck et al., 2010), following two exercise protocols: a pre-determined incremental protocol (up to 75% age-predicted HR_{max}), or a self-paced protocol (80% of age-predicted $HR_{max)}$ where participants chose their duration based on how long they felt they could go without exacerbating symptoms. Based on subjective ratings, all ME/CFS participants, despite the assigned protocol, were more sensitive to pain following exercise compared to controls who became less sensitive to pain (Van Oosterwijck et al., 2010).

It has been hypothesised that PEM may not occur following all types of exertion (Learmonth et al., 2014). No fatigue exacerbation or functional impairments were observed in an exercise study by Learmonth et al. (2014) involving a submaximal protocol (90% of calculated anaerobic threshold). This study utilised subjective measures (HADS scale and a fatigue/pain based scale) and objective functional measures (Timed 25 m walk and 3 m timed up and go test). The absence of PEM experienced here could be related to the submaximal protocol or the functional measures selected. Although these are generally considered valid measures of function, the exercise may not be long enough to

accurately capture the fatigue experienced by ME/CFS participants, as they likely take place well under the anaerobic threshold (Davenport et al., 2012; Learmonth et al., 2014).

Various physiological reasons for PEM have been proposed, including altered brain function, biochemical dysfunction and abnormal oxidative/immune stress, amongst many others (Cook et al., 2017; Nijs et al., 2014; Rutherford et al., 2016). Recent research has investigated PEM in detail to gather information on how it affects daily living and also to better understand its physiological basis (Jason et al., 2015). Many scholars are suggesting that those with ME/CFS may experience inappropriate or excessive skeletal muscle signalling following exertion, resulting in higher perceived fatigue or a higher sensitivity across fatigue pathways (Jones et al., 2010). Jones et al. (2010), reported following exercise that those with ME/CFS exhibited abnormalities in intramuscular pH recovery, expressing significantly higher muscular fatigue than controls, despite having very similar baseline pH measures. The prospect of over-sensitive muscular fatigue pathways was also investigated by Staud et al. (2015) whom supported the findings of Jones et al., (2010), indicating that peripheral tissues may play a part in PEM, whereby peripheral metabolites cause over-activation/sensitivity of fatigue pathways in ME/CFS (Staud et al., 2015). In a detailed literature review, Rutherford et al. (2016) identified extensive evidence to support biochemical dysfunction at the skeletal muscle level indicating that those with ME/CFS over-utilise lactate pathways during low intensity exercise (as low as 35% max exertion), and exhibit slow acid clearance abilities following exercise (Jones et al., 2010; Rutherford et al., 2016). A reduced ability to recover from exercise on a muscular level is a likely explanation for many aspects of PEM such as concentration and memory difficulties, wide-spread pain and a higher perception of, or susceptibility to fatigue following exertion (Rutherford et al., 2016; Staud et al., 2015).

Beyond muscular dysfunction, the immune response to exercise in ME/CFS is another potential reason for symptom exacerbation following exertion. Individuals with ME/CFS have shown an altered immune response, including an exacerbation of the immune and oxidative stress system when compared to healthy controls post-exercise. Specifically, research identifies exacerbated oxidative stress with a lack of anti-oxidant response, resulting in inefficient and ineffective immune processes following exertion (Nijs et al., 2014). Individuals with ME/CFS have been found to experience an abnormal gene

expression profile post-exercise, with higher levels of some immune cells, for example, the anti-inflammatory cytokine interleukin-10 (Nijs et al., 2014). Immune abnormalities and inflammation associated is a likely contributor to many symptoms of ME/CFS, including PEM, due to the relationship between immune cell elevation and fatigue (Montoya et al., 2017; Nijs et al., 2014). White et al. (2010) identified that ME/CFS patients who experienced greater increases in various cytokines following exercise, also experienced more profound symptom exacerbation, further supporting the notion that immune abnormalities are a cause for PEM.

Overall, PEM is a complex symptom where many, potentially overlapping, physiological processes are involved. More research is needed to clarify these processes and better understand why PEM occurs. Nonetheless PEM remains crucial as a definitive symptom. Post-exertional malaise is unique to ME/CFS and provides a rigorous starting point in differentiating ME/CFS as an isolated condition (Jason et al., 2015; Staud et al., 2015). Beyond causation, subjective investigations assessing PEM are becoming extensive; however additional objective studies are required to scientifically endorse PEM as a definitive symptom. Subjective studies are informative because they provide measures regarding increased fatigue however physiological studies on PEM are aimed at providing evidence as to its existence within ME/CFS and potentially, to warrant this symptom as a starting point for a diagnostic biomarker.

2.4 Exercise as Diagnosis

Due to the unique response that ME/CFS individuals have to exercise, it may provide a useful tool for diagnosis (Jason, Evans et al., 2015). Cardiopulmonary exercise testing has been identified by research as a potential method to objectively assess the clinical status of ME/CFS patients by evaluating and providing evidence of PEM (Twisk, 2014). An objective measure of PEM may help to improve diagnostic reliability using physiological information and consequently, working towards more recognition of those who suffer with ME/CFS (Jason et al., 2015). Physical therapists may play an important role in diagnosing ME/CFS with input from medical practitioners (Davenport et al., 2010). Before exercise testing can be implemented as a diagnostic tool, extensive research is needed to confirm its suitability and more specifically, investigate effective protocols (Keller et al.,

2014). In recent years researchers have placed a lot of focus on exercise testing for ME/CFS, to provide useful recommendations for ongoing research in the journey to effective diagnosis (Hodges et al., 2017).

In the forefront of this research, single maximal graded exercise tests have been investigated, but findings were inconsistent (Hodges et al., 2017). Some studies have suggested that a single test is appropriate to distinguish between ME/CFS and healthy populations, with others suggesting that testing needs to involve more than a single exercise test to truly capture PEM (Jones et al., 2012; Vanness et al., 2003). A single VO_{2max} exercise test was utilised in a study by Vanness et al., (2003), who reported that ME/CFS patients could be sub-classified using their VO_{2max} ($ml.kg.min^{-1}$) as a percentage of what they should be able to achieve. The categories were defined as: "mild impairment" (~56% males, 69% females), "moderate impairment" (46% males, 52% females) and "severe impairment" (30% males, 40% females) (Vanness et al., 2003). This study has a number of weaknesses; no controls were included and "normal" VO_{2max} values were based on a general normative cohort whom were not matched to ME/CFS participants and may not warrant accurate comparison.

Another study conducted by Wallman et al. (2004) matched controls and ME/CFS individuals, whom completed four single submaximal tests over four weeks (25W every minute up to 75% of age-predicted HR_{max}). Myalgic encephalomyelitis/chronic fatigue syndrome patients showed very similar physiological values to healthy controls throughout all phases of the exercise test except for the final phase, with no significant differences observed for heart rate, respiratory exchange ratio and oxygen uptake. However ME/CFS patients showed reduced ability to reach the target heart rate in the final stage and reported a significantly higher RPE throughout all phases of the test (see table 2). Due to subjective differences, authors proposed that exercise avoidance behaviours or an abnormal sense of effort might be related to the reduced capacity at the end stage (Wallman et al., 2004). It may be inaccurate to draw conclusions from submaximal values. Other researchers have indicated the importance of maximal exertion in highlighting these differences (Davenport et al., 2011).

Singular maximal exercise tests were assessed by Jones et al. (2012) and Vermeulen and Vermeulen Van Eck (2014). Both studies identified that ME/CFS patients have reduced exercise capacity in comparison to healthy controls. Not only at maximal capacity (VO_2 and workload) but also at the anaerobic threshold (AT) (VO_2) (Jones et al., 2012; Vermeulen & Vermeulen van Eck, 2014). Although this response is different from healthy individuals, research investigating functional capacity in other conditions, such as cardiovascular disease, identifies these same functional differences. These similarities are problematic when attempting to distinguish ME/CFS from other conditions via exercise testing (Aslanger et al., 2016). However, researchers still encourage single testing in ME/CFS to identify deconditioning; stating that the lower aerobic capacity within ME/CFS populations is more complicated. Jones et al. (2012), proposed a reduced capacity to normalise pH, with muscular pH levels within ME/CFS patients remaining elevated well beyond those of healthy controls, and Vermeulen and Vermeulen Van Eck (2014), proposed reduced uptake of oxygen by muscle cells in those with CFS. Both studies have shortcomings however, Vermeulen and Vermeulen Van Eck (2014), included a small control group in comparison to the ME/CFS group (203 vs. 18), raising questions on how well they were matched. Jones et al., (2012) had a small sample size where the study may have been statistically underpowered. It is evident that significant differences exist between studies, in regards to participant numbers, protocol types and the types of measures collected - displayed in table one. Therefore it remains difficult to draw any conclusions from these studies.

Table 1 Single exercise studies

Study	Number (n)	Diagnostic criteria used	Protocol	ME/CFS	Controls
Vaness et al., (2003)	189 ME/CFS 0 Controls	Holmes (1988)	Maximal single test Age: 19-60 yr. Gender: 137 F, 52 M	VO_{2max} range = 12.3-30.2 ml.kg.min^{-1}	
Wallman et al., (2004).	31 ME/CFS 31 Controls	Fukuda (1994) & medical diagnosis by doctor	Four maximal single tests (each 1week apart) Age: 22-64 yr. Gender: 9M, 22F	RER: 0.97 RPE: 16 HRmax%: 72 VO_2: 16.3 ml.kg.min^{-1} (mean of all tests)	RER: 1.03 RPE: 10 HRmax%: 75 VO_2: 19.9 ml.kg.min^{-1} (mean of all tests)
Jones et al., 2012	18 ME/CFS 12 Control	Fukuda (1994)	Incremental maximal test (cycle) Mean age – 44 yr. Gender: 2 M, 16 F	No values included	
Vermeulen & Vermeulen van Eck (2014)	203 ME/CFS 18 healthy	Fukuda (1994)	Incremental maximal test (cycle) Mean age – 37 yr. Gender – 178 F, 25 M	Female: AT = 10.9ml.kg.min^{-1} VO_2max = 20.3 ml.kg.min^{-1} Male: AT = 11.8 ml.kg.min^{-1} VO_2max = 24 ml.kg.min^{-1}	Female: AT= 13.7ml.kg.min^{-1} VO_2max = 27.4 ml.kg.min^{-1} Male: AT = 13.7 ml.kg.min^{-1} VO_2max = 27.3 ml.kg.min^{-1}

Key: F = female, M = male, AT = anaerobic threshold yr. = years old

Table 1: summary of key results from single exercise studies to date, outlining differences in functional capacity between healthy individuals and ME/CFS.

Despite inconsistencies, these findings suggest that ME/CFS patients exhibit a different response to exercise in comparison to healthy controls, with reduced physiological capacity to handle exertion (Jones et al., 2012). However, there is ongoing criticism regarding single exercise testing. Results could be categorised as similar to those of an unfit group of people and also, lack specificity to distinguish between ME/CFS and other conditions which also result in deconditioning (Snell et al., 2013). Furthermore, because experts are advocating the importance of PEM as a foundation symptom for diagnosis,

single-test protocols have been criticised to not reflect PEM, as symptoms will only occur "post-exertion". Therefore a single test is circumventing what could be crucial observations following the initial exertion (Ciccolella et al., 2007).

Discrepancies in single exercise testing have led researchers to investigate responses utilising repeated exercise protocols. To-date, the majority of this research appears to be including 24-hour repeated protocols. Participants complete an incremental maximal exercise test and then return 24-hours later to complete an identical test. A 24-hour repeated protocol was utilised by Davenport et al., (2011) where a subjective questionnaire evaluated the exacerbation of symptoms following both exercise tests. Results indicated that ME/CFS subjects had not recovered when they returned 24 hours later with some individuals taking up to 7-days to recover (Davenport et al., 2011). Thus, a recovery time of more than 24-hours could be suitable in diagnostic criteria for ME/CFS, however with only subjective information problems still remain regarding validity (Davenport et al., 2011).

From a physiological perspective, a pilot study by VanNess et al. (2007), also examined a 24-hour repeat test. No differences were evident in measures (at AT and VO_{2max}) between groups on day one, however 24-hours later, significant differences were observed. At both maximal exercise and AT, VO_2 ($ml.kg.min^{-1}$) decreased in the ME/CFS group and increased in the control group. Similar findings were observed in another study by Vermeulen et al. (2010). Although ME/CFS patients exhibited reduced fitness levels on both days, these findings were emphasised after 24-hours, with a further decline in functional capacity in the ME/CFS group alone (Vermeulen et al., 2010). A decrease in achievable workload (W) at the AT, was significant in contrast to a notable improvement of the control group. These results are presented in table 3. The decrease in functional capacity after 24-hours in ME/CFS populations has been re-produced in many other studies; Snell et al., (2013) and Keller, Pryor and Giloteaux (2014) both observed further declines in functional capacity at the second exercise test. Furthermore, findings of these studies indicate that functional capacity would be over-estimated in the majority of participants if a single test were used. Collectively, exercise studies are providing consistent evidence for the importance of a repeated protocol; many scholars argue that only a repeated test will emphasise PEM and the recovery implications of this symptom (Keller et al., 2014; Snell et al., 2013).

Although 24-hour repeated protocols are providing notable progress from single test studies, there remains inconsistencies within the methodology of these protocols. One of the major inconsistencies observed is the different submaximal measures, with some studies reporting values at the AT and others reporting values at the respiratory exchange ratio (RER). For example, in table two Hodges et al., (2017), reported submaximal VO_2 values significantly higher than other studies due to these values being calculated at RER (1.0) and not at AT. Both methods have been validated as reliable measures of submaximal fitness, however other researchers suggest that AT (or ventilatory threshold, VT) may be more suitable when investigating diseased populations, compared to RER (Wasserman et al., 1994; Williamson et al., 2012).

Table 2 Summary of Repeated Exercise Studies (24-hour)

Study	Selection Criteria	Sample size	AT or RER ($\boldsymbol{VO_2}$ml.kg.min^{-1})		Max ($\boldsymbol{VO_2}$ml.kg.min^{-1})		Workload at AT or RER (W)	
Vanness et al., 2007	Fukuda (1994) + referral from physician	6 ME/CFS 6 Ctrl	ME/CFS: 1: 15.01 2: 11.01	CTRL 1: 17.55 2: 18.00	ME/CFS: 1: 26.23 2: 20.43	CTRL 1: 28.43 2: 28.90		
Vermeulen et al., 2010	Fukuda (1994)	15 ME/CFS 15 Cont	ME/CFS: 1: 12.8 2: 11.9	CTRL 1: 16.7 2: 18.0	ME/CFS: 1: 22.3 2: 20.9	CTRL 1: 31.2 2: 30.9	ME/CFS: 1: 58.6 2: 54.5	CTRL: 1: 82.9 2: 92.2
Snell et al, 2013	Fukuda (1994) +required PEM	51 ME/CFS 10 Ctrl	ME/CFS: 1. 12.74 2. 11.36	CTRL 1. 13.83 2. 14.12	ME/CFS: 1. 21.51 2. 20.44	CTRL 1. 25.04 2. 23.96	ME/CFS: 1: 49.51 2: 22.20	CTRL 1: 58.00 2: 63.50
Keller et al., 2014	Fukuda (1994)	22 ME/CFS 0 Ctrl	ME/CFS: 1. 12.2 2. 9.9		ME/CFS: 1. 21.9 2. 18.6		ME/CFS: 1. 51.4 2. 41.4	
Hodges et al., 2017	Fukuda (1994) + CCC + ICC	10 ME/CFS 10 Ctrl	ME/CFS: 1. 20.95 2. 22.22	CTRL 1. 23.55 2. 28.45	ME/CFS: 1. 24.95 2. 26.27	CTRL 1. 31.99 2. 33.06	ME/CFS: 1. 105 2. 93	CTRL 1. 119 2. 132

Key: 1 = day 1, 2 = day 2, CFS= Chronic Fatigue Syndrome, ME= Myalgic encephalomyelitis, Ctrl = controls, AT = anaerobic threshold RER = Reparatory exchange ratio, CCC = Canadian consensus criteria, ICC = International consensus criteria

Another important factor to consider is whether this functional decline following an initial bout of exertion, is also evident in other health conditions. Prominent symptom cross-over with other conditions is a problematic aspect of ME/CFS diagnosis, hence if repeated exercise protocols were to be implemented, the ME/CFS response must differ significantly to that of other health conditions (Jason et al., 2015). A recent study by Hodges et al. (2017) evaluated the suitability of a 24-hour protocol by comparing ME/CFS responses to those of MS participants as well as healthy controls. This study observed a significant decline in workload at RER after 24-hours in the ME/CFS group (Hodges et al., 2017). It was also identified that MS participants, like ME/CFS, were deconditioned at the initial test, but unlike ME/CFS, MS participants showed improvements in functional capacity after 24-hours (Hodges et al., 2017). This study supports the use of a 24-hour repeated protocol to measure physiological aspects of PEM and provides evidence that PEM is unique to ME/CFS as a condition.

Research directly comparing ME/CFS to other fatigue related conditions appears to be sparse. White et al. (2012) compared exercise responses in ME/CFS, MS and healthy controls. Blood sampling, fatigue and pain ratings were collected at baseline and then 30 minutes, 8-hours, 24-hours and 48-hours following an exercise protocol on a cycle ergometer (20-minutes at 70% age-predicted HR_{max}). Results showed that both MS and ME/CFS have higher baseline fatigue and pain, and both show similar immune response to exercise short-term (>8 hours). However, ME/CFS participants experienced significantly higher pain ratings up to 48-hours after exercise, whereas MS participants and healthy controls did not (White et al., 2012).

Studies investigating the acute response to exercise in MS consistently report positive findings; unlike ME/CFS, those with MS experience a number of benefits following exercise, both acutely and chronically (Ensari, Sandroff, & Motl, 2017). Exercise has been deemed a viable part of treatment for managing fatigue in MS patients, due to its proven capability to reduce fatigue overtime (Petruzzello & Motl, 2011). Furthermore, it has been found that exercise across a range of intensities (40-70% HR_{max}) improves mood and vigour without worsening fatigue post-exercise in the short term as well (Ensari et al., 2017; Petruzzello, Snook, Gliottoni, & Motl, 2009). Therefore, exercise testing may effectively distinguish between ME/CFS and MS if it is implemented as a diagnostic tool.

Fibromyalgia is another condition often associated with ME/CFS; literature suggests that both conditions have similar behaviours towards exercise, due to the common pain experienced (Nijs et al., 2013). To-date research on fibromyalgia and exercise is sparse, however Mengshoel et al. (1995), reported that participants with fibromyalgia experienced significantly higher extremity pain during and following a submaximal exercise test as well as higher exercising RPE compared to controls. A similar response was observed following a maximal exercise study with fibromyalgia patients also experiencing significantly higher pain ratings post-exercise (Nørregaard, et al., 1994). However, there were no measures of fatigue specifically in either of these studies - an important measure in regards to ME/CFS comparison (Nørregaard et al., 1994; Mengshoel et al., 1995). The potential similarities between ME/CFS and fibromyalgia are problematic in regards to the validity of exercise testing to differentiate the two conditions. However, the few studies that have examined fibromyalgia post-exercise are out-dated and no studies have compared ME/CFS and fibromyalgia directly, using repeated exercise protocols. Further research is required to determine whether the objective measures observed in ME/CFS studies are effective to distinguish them from fibromyalgia patients.

There is some consensus regarding the unique 24-hour response to exercise with ME/CFS and potentially some measurements for diagnosis, – although there is little objective research beyond 24-hours. Subjective studies suggest that PEM may extend well beyond this point, and perhaps decline further after 24-hours (Lindheimer et al., 2017). A study by Yoshiuchi et al. (2017) found that physical symptoms declined following maximal exercise, but the most significant impairments were evident after a 5-day delay, supporting the notion that PEM lasts well beyond 24-hours. Recently, the timeline of PEM was examined following a singular maximal exercise test, at 48 and 72-hours. Results revealed that ME/CFS patients still had significantly higher general fatigue, muscular fatigue, mood disturbance and confusion and significantly reduced motivation levels at both 48 and 72-hours according to subjective information (Lindheimer et al., 2017). Although, not all exercise studies have observed PEM beyond 24-hours. Keech et al., (2015), found that fatigue was elevated immediately following the exercise test and returned to baseline at 72-hours post-exercise. Similar findings were reported in an

earlier study (Bazelmans, et al., 2005); following a maximal test, fatigue was most elevated at 48-hours and at 72-hours had returned to baseline.

Exercise protocols as a diagnostic tool are gaining credibility, however the timeline of PEM needs to be well-defined to develop a protocol that will capture PEM at its most severe stage (Hodges et al., 2017). Subjective measures are useful to gain preliminary knowledge, however results appear to be unclear as to how long PEM lasts, with studies offering a vast range of timelines. Objective measures beyond 24-hours are required to better illustrate and consolidate the timeline of PEM from a physiological perspective (Twisk, 2014). By scientifically assessing function beyond 24-hours, it will provide further knowledge of how long PEM lasts and also, the most definitive point along this timeline in regards to what type of protocol would provide the best diagnosis.

2.5 Treatment

The ultimate goal behind accurate diagnostic methods is to provide scientific evidence for treatment strategies for those with ME/CFS (Jason et al., 2012). Currently, methods of treatment for ME/CFS vary, with little consistency across the medical field (Worm-Smeitink et al., 2016). Since the discovery of CFS, initial treatment has commonly involved the independent management of specific symptoms with appropriate medication or minor lifestyle changes such as a reduction in physical activity (Yancey & Thomas, 2012). Although traditional treatment methods may be somewhat helpful, there is little evidence to support their ongoing implementation. Due to the need for more effective treatment, two alternative treatment methods are gaining credibility; cognitive behavioural therapy (CBT) and graded exercise therapy (GET) (Yancey & Thomas, 2012).

CBT is a psychological method that places focus on the mental factors that may pre-dispose or perpetuate the effects of ME/CFS, for example negative emotions, poor stress management and 'all or nothing' behaviour types (Fernie et al., 2015). Cognitive behavioural therapy aims to reduce "fear-avoidance" behaviours by making patients aware of these behaviours and how they may contribute to the way they are feeling (Yancey & Thomas, 2012). Some researchers and clinicians are critical of CBT, suggesting that the theory behind it is accusational and overlooks the potential physiology involved

(Fernie et al., 2015). Despite this view, the majority of research is in support of CBT, with many studies observing positive treatment outcomes (Yancey & Thomas, 2012). The effectiveness of CBT has been investigated by Flo and Chalder (2014). Results demonstrated that 37.5% of patients met recovery and 18.3% met "full" recovery after 6-months of CBT. Worm-Smeitink et al. (2016) also observed reductions in fatigue and disability for patients who committed to a period of CBT.

In contrast to CBT, Graded Exercise Therapy (GET) adopts a physical approach to treatment where deconditioning is the central cause for ME/CFS and its associated symptoms (Yancey & Thomas, 2012). The theory of GET proposes that after an initial physical or emotional trigger (i.e. a virus) ME/CFS symptoms decline further in a cycle of deconditioning. Graded exercise therapy therefore aims to reverse the effects of deconditioning by gradually improving physical function (Fernie et al., 2015). Supporters of GET advocate that it is the most appropriate method of exercise for ME/CFS treatment, as it allows patients to initially work at an intensity and duration that will not exacerbate symptoms, by implementing a target heart rate zone, and increase the intensity and/or duration parallel to individual improvements in functional capacity (Fernie et al., 2015; Yancey & Thomas, 2012). Research investigating GET is less prominent than that investigating CBT, likely due to the negative effects commonly associated with ME/CFS and exertion, and therefore the higher risk associated with exercise trials and ME/CFS. Although the theory of GET is well supported, it is difficult to distinguish what exercise intensity, duration and frequency elicits ME/CFS symptom exacerbation (White et al., 2011). Graded exercise therapy is normally undertaken only weekly or fortnightly and involves close monitoring (Fernie et al., 2015).

The PACE trial (2011), short for "Pacing, graded Activity, and Cognitive behaviour therapy; a randomised Evaluation", is one of the more comprehensive studies investigating treatment methods. The study included both GET and CBT, with Adaptive Pacing Therapy (APT), another proposed method of treatment which aims to manage and increase energy levels overtime (White et al., 2011). Adaptive pacing therapy involves a daily diary to manage daily tasks and rest, to increase physical activity whilst avoiding over-exertion and symptom exacerbation (White et al., 2011). Results of the PACE trial support the use of both CBT and GET; both protocols reported that 41% of patients

improved their overall health after 52-weeks (White et al., 2011). Adaptive pacing therapy and specialist medical care alone were less effective, with 31% and 25% of patients seeing improvements respectively. Furthermore, APT was not recommended due to a significantly higher amount of adverse effects than other protocols, further highlighting the sensitivity required when promoting physical activity for ME/CFS. Although results were positive for the use of GET, there has been a level of criticism toward the PACE trial. For example, Dougall et al., (2014) closely examined results, identifying occurrences of serious adverse effects, minor symptom exacerbation and frequent minor adverse effects. This included GET participants, with 11% experiencing frequent adverse effects. It is difficult to determine whether this is due to the treatment protocols or the nature of the illness itself that naturally involves a series of adverse and unpredictable events. It is also important to note, that since it's publication, the credibility of the PACE trial has been questioned extensively; investigations suggesting potentially biased statistical analysis and presentation (Geraghty., 2017). More research is needed before GET can be implemented as a widespread method of treatment (Dougall et al., 2014).

Overall, it appears that until we have a clear understanding of how ME/CFS patients respond to exercise, it is unlikely that we will be able to prescribe exercise effectively as a means of treatment (Twisk, 2014). Furthermore, without rigorous diagnostic tools, it is unclear whether those participating in ME/CFS treatment trials have the same medical condition, or classification and therefore diagnosis should be a focal point of research at this stage. Additionally, practical knowledge of PEM, its timeline and how ME/CFS respond to accumulative exercise efforts is required to develop well-researched protocols before long-term treatment trials can take place effectively (Hodges et al., 2017). The potential value of exercise testing in this population is obvious, however further knowledge is mandatory before we can use this tool effectively and safely. The ongoing progression of acute exercise studies will provide the details needed to move forward, not only in accurately diagnosing ME/CFS but also in taking a crucial step towards effective treatment options for individuals with ME/CFS.

CHAPTER THREE: AIMS AND HYPOTHESES

3.1 Introduction

From the literature review it has been clearly identified that an area requiring further investigation is the timeline of PEM and its application in ME/CFS diagnosis. It is evident from the literature that current diagnostic methods have several disadvantages and therefore, ME/CFS diagnosis requires scientific validation. Repeated exercise protocols have provided evidence of a functional decline during PEM, but the timeline of this decline is yet to be determined with a small number of studies examining beyond 24-hours. Therefore, the purpose of this study was to investigate the timeline of PEM via physiological and subjective aspects, following 48-hour and 72-hour repeated exercise protocols, to determine their suitability for diagnostic purposes.

3.2 Aims

Specifically, the following aims were:

1. To gain new information of objective and subjective measures on the nature and timeline of post-exertional malaise.
2. To assess the suitability of a 48-hour and a 72-hour repeated exercise protocol for the diagnosis of ME/CFS.

3.3 Hypotheses

It was hypothesised that following a maximal exercise test PEM and functional capacity would further decline at 48-hours compared to the initial exercise test and will remain declined at 72-hours.

As a secondary hypothesis, it was proposed that following a maximal exercise test, subjective measures of fatigue will vary significantly between participants.

CHAPTER FOUR: MATERIALS & METHODS

4.1 Experimental Overview

The study was designed as a case-controlled comparison, as this study type is ideal for directly comparing populations with and without a particular condition (Lewallen & Courtright, 1998). Initially, 20 ME/CFS participants were recruited for the study; however three were unable to participate in the entire protocol, and one withdrew prior to the first exercise test. In total, 16 ME/CFS participants and 16 age and gender matched controls took part in the study. All participants were randomly assigned to one of two groups; a 48-hour group (n=8 ME/CFS and n=8 controls) or a 72-hour group (n=8 ME/CFS and n=8 controls).

All participants completed a daily diary of fatigue for 7-days prior to their participation (see appendix 9.2). Each participant completed a maximal exercise test on day one (baseline test) and repeated this either 48-hours or 72-hours later (post-test), based on the group they were assigned to. Participants completed a daily diary of fatigue for 10-days following the second exercise test, as well as specific exercise recovery questions (see appendix 9.3). For ease of participant accessibility, testing was conducted at three locations: Massey University mobile exercise laboratory in Tauranga (New Zealand) July 2017 (n= 10 CFS and n=3 Controls), Massey University Wellington campus, laboratory 3C26, (New Zealand) September 2017 (n = 6 ME/CFS) and the Manawatu campus, human performance laboratory (New Zealand) September 2017 (n=13 controls). All testing was conducted with the same equipment. The Central Health and Disability Ethics Committee approved the study on the 30th of March, 2017 (reference 17NTA/47).

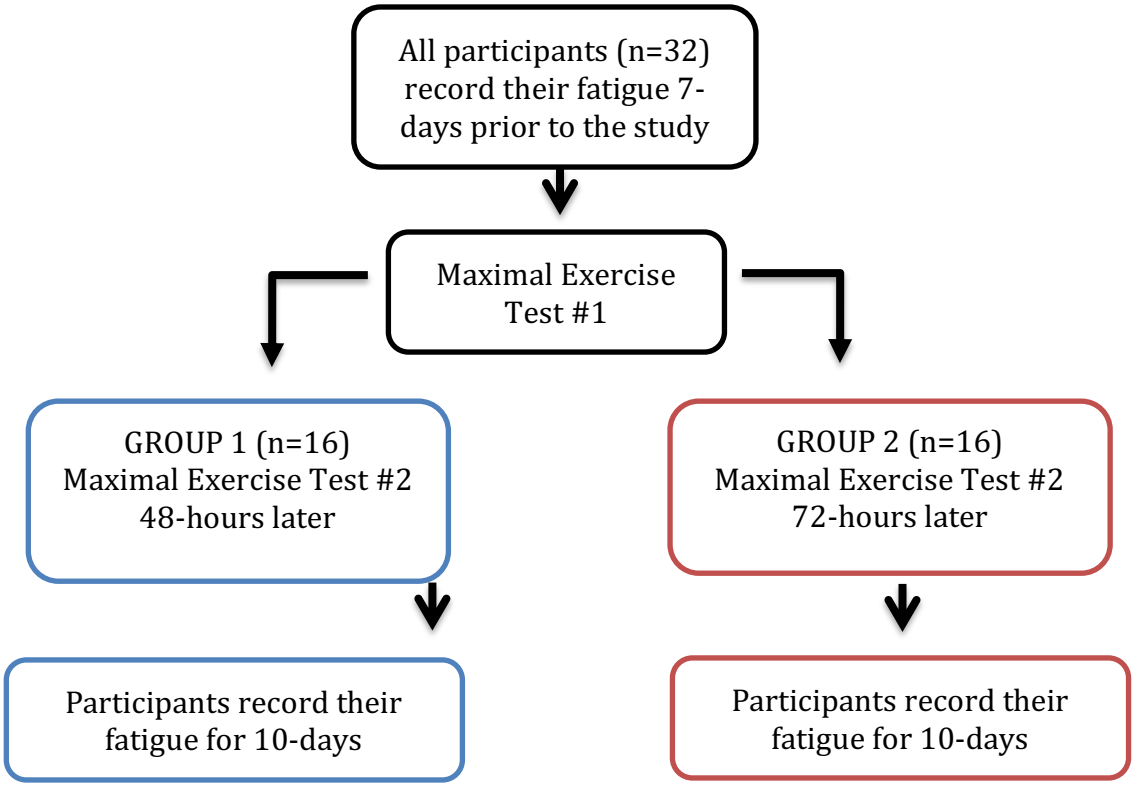

Figure 1 General overview of the testing procedure, including controls and ME/CFS.

4.2 Participant Recruitment

The ME/CFS participants were recruited through the Tauranga ME/CFS Society via a presentation by Dr Lynette Hodges and a follow-up email; other participants were recruited through contact with the Associated New Zealand ME Society (ANZMES). Individuals who were interested in participation completed an online De Paul Symptom and SF-36 screening questionnaire and responses were analysed using the International Consensus Criteria. This criteria was selected due to its midway sensitivity in comparison to other available criteria (see section 2.2). Volunteers who met the criteria were invited to participate in the study. Control participants were recruited through email by acquaintance of ME/CFS participants, acquaintance of researchers or sourced from the Massey University staff database. Controls were matched to ME/CFS participants by gender and age (2 years either side) and effort was made to match controls of similar activity levels. All participants were provided with a detailed information sheet at least 2 weeks prior to the study and completed a health/medical history questionnaire, an informed consent and a pre-exercise

questionnaire (see appendix 9.1) to confirm their suitability for participation. Exclusion criteria for both controls and ME/CFS participants included symptomatic heart failure, unstable angina, symptomatic peripheral arterial disease, dementia or aphasia and any other medical conditions that prohibit aerobic exercise (ACSM, 2014). Furthermore, we excluded anyone with history of fibromyalgia and/or depression due to high symptom crossover with ME/CFS.

4.3 Procedures

Prior to participation, participants were instructed to avoid food or smoking for 2-hours and caffeine for 4-hours. They were also instructed to avoid exercise 24-hours prior to the exercise test. Seven days prior to the first maximal exercise test participants were provided with a subjective questionnaire, known as the daily diary of fatigue (see appendix 9.2). The online gas-analysis system turbofit (version 15, Vacu Med, Ventura CA, USA) was calibrated within 30 minutes prior to each exercise test. The laboratory environment remained a constant temperature of 17-18°C and barometric pressure was recorded prior to every test.

Following a seated period of 5 minutes, blood pressure (BP) was measured using a sphygmomanometer and stethoscope. Height was then measured using a stadiometer (Seca, Bonn, Germany; accurate to 0.1cm) and body mass measured using electronic scales (Hiweigh technologies Ltd, Shanghai, China; model X3, accurate to 0.02kg), and body mass index (BMI) was estimated from these measures (Keys et al., 1972). A Polar HR monitor (Polar FS1, Polar Electro, Finland) was fitted to participants and resting heart rate was recorded. The computer-controlled cycle ergometer (Excalibur sport, Lode, Netherlands), was setup to the correct height (approximately a 5 degree bend at the knee) for each participant. The Borg 6-20 RPE scale (Borg, 1982) and the testing protocol was explained to each participant.

Directly before the test started, the mouthpiece and nose clip were fitted to the participant and adjusted accordingly, the participant started cycling and maintained a rate of 60-70 revolutions per minute (rpm). The exercise test started at a load of 15 W and increased by 15 W every minute until the participant was unable to continue, requested to stop or met any of the ACSM (2014) termination criteria (including onset

of angina-like symptoms, a drop in systolic blood pressure by >10mmHg, excessive rise in BP >250/115mmHg, signs of poor perfusion or abnormal HR response). During the maximal exercise test heart rate and RPE (Borg scale, 6-20) were recorded during the last 15 seconds of every minute and BP recorded every 3 minutes. Oxygen consumption ($ml.kg.min^{-1}$), carbon dioxide production (L.min) and respiratory exchange ratio (RER) were collected by breath-by-breath using a two-way breathing valve in 10-second intervals, using the online analysis system, turbofit (version 15, Vacu Med, Ventura CA, USA).

All tests were termed maximal by meeting at least two of ACSM's criteria; a plateau in VO_2 consumption, an RER of more than 1.10, HR within 10bpm of age-predicted max and an RPE of greater than 17 on the Borg scale (ACSM, 2014). At the termination of testing, a warm-down was performed where the load was reduced to 15 Watts and the participant continued cycling for 5-minutes or until HR and BP returned to within 20bpm and 10mmHg of resting measures.

Participants returned either 48 or 72-hours later where all procedures were repeated. On completion of the second test, participants were provided with a take-home daily diary of fatigue (see appendix 9.2), identical to that provided before the study, which they completed for 10 consecutive days.

4.4 Statistical Analysis

Measures of oxygen uptake (VO_2), carbon dioxide elimination (CO_2), respiratory exchange ratio (RER) and expiratory minute ventilation (V_E) were recorded and extracted in 10-second intervals using the online system. Mean values of each minute were calculated and recorded for every participant and collated with manually collected measures of HR, BP and RPE. Workload and VO_2 were calculated at an RER of 1.0, based on minute-by-minute mean data. Workload and VO_2 at AT were calculated using the V-slope method, by plotting VO_2 uptake against CO_2 output for each test and manually identifying the point of departure from linearity. Subjective measures of fatigue pre and post-test (rated 1-10) and total time to recover (days) was collated from the participant diaries of fatigue. Data was analysed using paired sample t-tests (2-tailed) to identify differences between ME/CFS participants and their controls and

independent sample t-tests to identify differences between the initial test and the repeated test (48-hours or 72-hours). Variables selected for analysis were based on those objective measures identified as important among previous repeated studies (Hodges et al., 2017; Vermeulen el al., 2010; VanNess et al., 2007; Keller et al., 2014).

Data for all groups were assessed for normality using the Kolmogorov-smirnov test of normality. The sample size of the present study was calculated from previous research of Hodges et al. (2017) where the VO_2 at anaerobic threshold for ME/CFS was 22.20 ml.kg.min^{-1} and healthy controls was 28.45 ml.kg.min^{-1}, with a standard deviation of 6.1 for the ME/CFS group. Thus, with a power of 80% and a significance level of 0.05, a sample size of 16 was required. All data was analysed using the statistical package for social sciences (SPSS version 25.0, IBM, New York, USA) with statistical significance set at $p < 0.05$. Results are reported as mean (standard deviation).

CHAPTER FIVE: RESULTS

5.1 Participant Characteristics

Table three displays participant characteristics. From the sample of 32, there were 10 males (31%) and 22 females (69%), the higher ratio of females is normal for ME/CFS populations (Faroa et al., 2015). There was one male in each of the 48-hour groups, compared to four males in the 72-hour groups; the difference in height and weight may be attributed to this gender difference. Body mass index is however similar across all groups. Baseline fitness levels from the two ME/CFS groups were similar to each other, as well as the two control groups. As expected there were differences in baseline fitness between controls and ME/CFS participants ($p > 0.05$).

Table 3 Mean (SD) of participant characteristics

	ME/CFS48H n =8	CTRL48H n = 8	P-value	ME/CFS72H n = 8	CTRL72H n = 8	P-value	ALL n = 32
Age (years)	41 (13.6)	42 (12.8)	0.87	54 (7.1)	53 (7.2)	0.78	47 (11.9)
Height (cm)	163.6 (6.2)	164 (8.7)	0.92	174.3 (10)	171.2 (9.7)	0.62	168.3 (9.6)
Weight (kg)	68.74 (12.1)	70 (16)	0.88	78.9 (14.3)	77.1 (16.4)	0.87	73.7 (14.9)
BMI ($kg\,m^2$)	25.5 (3.1)	25.9 (4.5)	0.9	25.9 (4.2)	26.2 (3.2)	0.94	25.9 (3.6)
$VO_{2\,max}$ ($ml.kg.min^{-1}$)	25.9 (3.6)	38.8 (3.6)	**0.01**	23.7 (8.7)	30.9 (6.9)	0.09	

Key: ME/CFS48H = ME/CFS 48-hour; CTRL48H = controls 48-hour; ME/CFS72H = ME/CFS 72-hour; CTRL72H = ME/CFS 72-hour; n = number

5.2 Physiological Results

Table four displays maximal physiological results of both exercise tests across all groups (48-hour and 72-hour). The data shows significant differences between groups in both protocols for VO_{2max} ($ml.kg.min^{-1}$) and workload (W); ME/CFS showed significantly lower values at both tests compared to their controls (48-hour p= <0.05, 72-hour p= <0.05). The 72-hour protocol alone showed significant differences in heart rate between groups (at both the baseline test and the post-test) and RER (at baseline alone), with ME/CFS having a lower heart rate and RER than their controls. The 72-

hour ME/CFS group reached maximal exercise at 80% of their age-predicted heart rate max, while the 48-hour group reached maximal exercise at 89% of their age-predicted heart rate max. Both control groups reached maximal exercise closer to their age-predicted max, at 93% (48-hour protocol) and 96% (72-hour protocol). Between days, there were no significant changes observed in any group.

Table 4 Mean (SD) maximal data of physiological variables from maximal cycle test at baseline and at 48 and 72-hours

	ME/CFS48h (n=8)	CTRL48h (n=8)	*P value* (grp)	ME/CFS72H (n=8)	CTRL72h (n=8)	*P value* (grp)
$VO_{2\ max}$ (ml.kg.min^{-1})						
D1	25.9 (3.6)	38.8 (3.6)	***0.02****	23.7 (8.7)	30.9 (6.9)	*0.09*
D2	24.5 (5.6)	36.7 (9.9)	***0.02****	23.8 (7.6)	32.4 (8.0)	***0.05****
P value (days)	*0.26*	*0.46*		*0.92*	*0.50*	
Workload (watts)						
D1	116.3(29.7)	178.1 (25.9)	***0.001****	114.4 (41.6)	170.6 (60.5)	***0.05****
D2	114.4 (29.9)	183.7 (36.5)	***0.001****	125.6 (39.2)	176.3 (58.8)	*0.07*
P value (days)	*0.685*	*0.351*		*0.285*	*0.285*	
RPE (6-20)						
D1	17 (1.2)	16 (3.2)	*0.76*	17 (1.2)	17 (1.4)	*0.71*
D2	17 (0.9)	17 (3.4)	*0.56*	18 (0.8)	17 (1.5)	*0.12*
P value (days)	*0.80*	*0.44*		*0.22*	*1.00*	
HR (bpm)						
D1	162 (14)	165 (18)	*0.75*	133 (27)	160 (17)	***0.03****
D2	160 (12)	164 (25)	*0.69*	133 (21)	160 (13)	***0.01****
P value (days)	*0.60*	*0.76*		*0.875*	*1.00*	
RER						
D1	1.1 (0.1)	1.1 (0.1)	*0.97*	1.03 (0.1)	1.1 (0.04)	***0.05****
D2	1.1 (0.1)	1.1 (0.1)	*0.52*	1.1 (0.1)	1.1 (0.06)	*0.70*
P value (days)	*0.56*	*0.68*		*0.46*	*0.12*	

Key: D1 = baseline test; D2 = post-test (48 or 72 hours later); ME/CFS48H = ME/CFS 48-hour group; CFS72H = ME/CFS 72-hour group; CTRL48H = Controls 4-hour group; CTRL72H = Controls 72-hour group; grp = differences between groups.

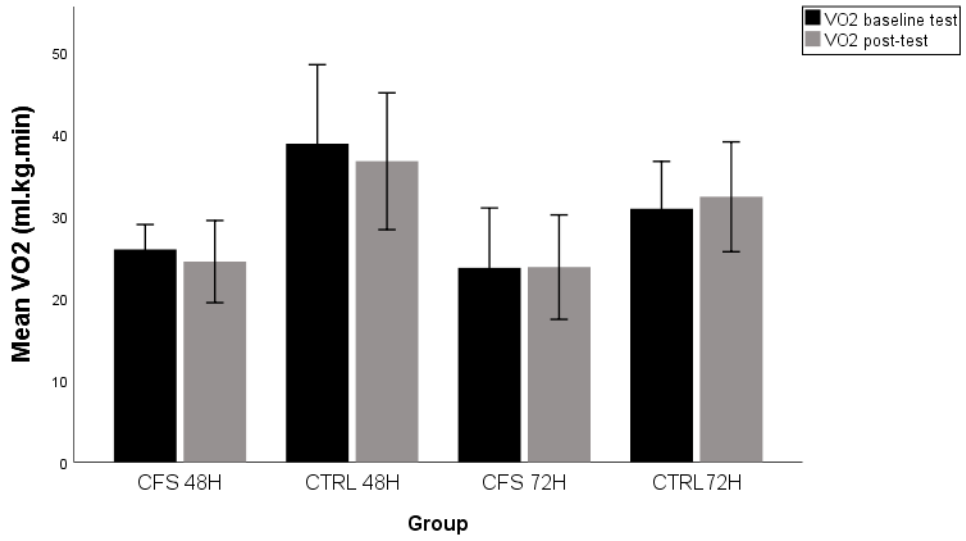

Figure 2 Mean VO_2 (ml.kg.min^{-1}) at Maximal Exercise for baseline test and post test. Error bars represent the standard deviation.

Figure 2 illustrates the differences in VO_2 at maximal exercise between ME/CFS groups and controls, and small changes in $VO_{2\,max}$ between the baseline test and the post test, for all groups.

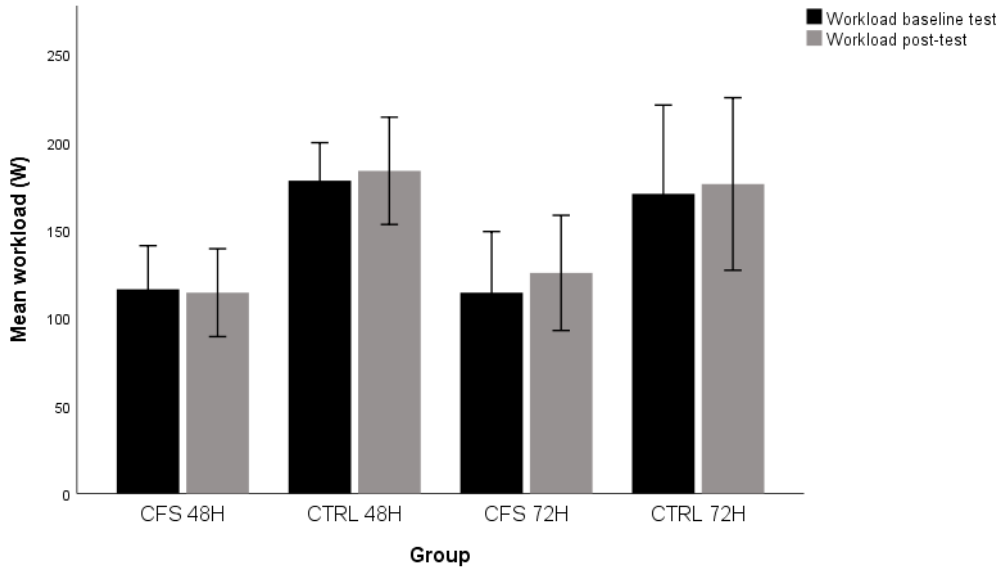

Figure 3 Mean workload (W) at Maximal Exercise for baseline test and post test. Error bars represent the standard deviation.

Figure 3 illustrates the differences in maximal workload (W) between ME/CFS and controls, but also demonstrates the absence of any significant changes in load at both 48-hours and 72-hours.

Table five displays results from analysis data at RER (1.0) of both exercise tests (baseline and post-test) across all four groups. In regards to the 48-hour protocol, RER data shows significant differences in both VO_2 at RER ($ml.kg.min^{-1}$) (p-value <0.05) and workload (W) (p-value <0.01), indicating that this ME/CFS group had a lower RER than their control group both at baseline and at 48-hours. For the 72-hour protocol there were no significant differences in these measures at RER between groups, however both $\%VO_{2\ max}$ and RPE at RER were significantly different across groups (p-values = <0.05). The 72-hour ME/CFS group had a significantly higher RPE than their controls at RER (despite a similar workload) and reached RER at a significantly lower percentage of their $VO_{2\ max}$ both at baseline and at 72-hours.

Across days, there were also differences at RER. Both control groups reached RER closer to their maximum VO_2 at the post-test; the 48-hour control group increased their $\%VO_{2\ max}$ (p-value=0.01) and the 72-hour control group showed an increase in achievable workload (and therefore efficiency) (p-value = 0.013). The 72-hour ME/CFS group also showed this response, with an increase in workload of 13.12 watts at the 72-hour test but this increase in workload is only approaching significance (p = 0.087). The 48-hour ME/CFS group did not show any changes across days but was able to achieve the same workload after 48-hours with no decline observed (p = 1.00).

Table 5 Mean (SD) Submaximal data collected at the respiratory exchange ratio (1.0) at baseline, 48-hours and 72-hours

	ME/CFS48h (n=8)	CTRL48h (n=8)	P-value (grp)	ME/CFS72H (n=8)	CTRL72h (n=8)	P-value (grp)
VO_2 @ RER ($ml.kg.min^{-1}$)						
D1	21.2 (5.6)	31.1 (6.6)	***0.006****	21.1 (8.4)	23.5 (4.5)	*0.49*
D2	21.3 (6.9)	31.9 (8.9)	***0.02****	21.6 (7.7)	23.7 (4.4)	*0.52*
P-value *(days)*	*0.95*	*0.702*		*0.587*	*0.89*	
$\%VO_{2max}$ (%)						
D1	81.5 (15.8)	82.8 (14.6)	*0.87*	88.1 (11.8)	77.1 (12.8)	***0.04****
D2	86.2 (10.5)	87.8 (11.5)	*0.8*	91.2 (9.9)	75.4 (13.3)	***0.04****
P-value *(days)*	*0.32*	***0.01****		*0.58*	*0.49*	
Workload @ RER (W)						
D1	88.1 (37.9)	146.2 (20.8)	***0.003****	99.4 (43.9)	95.6 (26.5)	*0.84*
D2	88.1 (33.5)	157.5 (36.7)	***0.001****	112.5 (34.9)	129.3 (46)	*0.42*
P-value *(days)*	*1.00*	*0.265*		*0.087*	***0.013****	
Efficiency ($watts/VO_2$)						
D1	4.1 (0.9)	4.9 (1.0)	*0.2*	4.8 (0.9)	4.1 (0.9)	*0.34*
D2	4.2 (0.9)	5.1 (1.0)	*0.18*	5.3 (1.1)	5.3 (1.2)	*0.96*
Sig (days)	*0.51*	*0.33*		*0.17*	***0.008****	
RPE @ RER (6-20)						
D1	15 (1.7)	14 (2.9)	*0.54*	16 (2.0)	12 (1.7)	***0.001****
D2	15 (1.6)	14 (3.3)	*0.61*	17 (1.9)	14 (1.6)	***0.003****
P-value *(days)*	*0.32*	*0.53*		*0.35*	*0.03*	
HR (bpm)						
D1	146 (21)	151 (14)	*0.64*	124 (24)	121 (12)	*0.82*
D2	144 (15)	152 (22)	*0.37*	127 (18)	138 (8)	*0.14*
P-value *(days)*	*0.64*	*0.68*		*0.51*	*0.43*	
RER						
D1	1.0 (0.02)	1.0 (0.3)	*0.1*	1.0 (0.5)	1.1 (0.1)	*0.22*
D2	1.0 (0.1)	1.0 (0.1)	*0.7*	1.1 (0.1)	1.0 (0.1)	*0.59*
P-value *(days)*	*1.0*	*0.47*		*0.14*	*0.10*	

Key: D1 = baseline test; D2 = post-test (48 or 72 hours later); ME/CFS48H = ME/CFS 48-hour group; ME/CFS72H = ME/CFS 72-hour group; CTRL48H = Controls 48-hour group; CTRL72H = Controls 72-hour group; grp = differences between groups

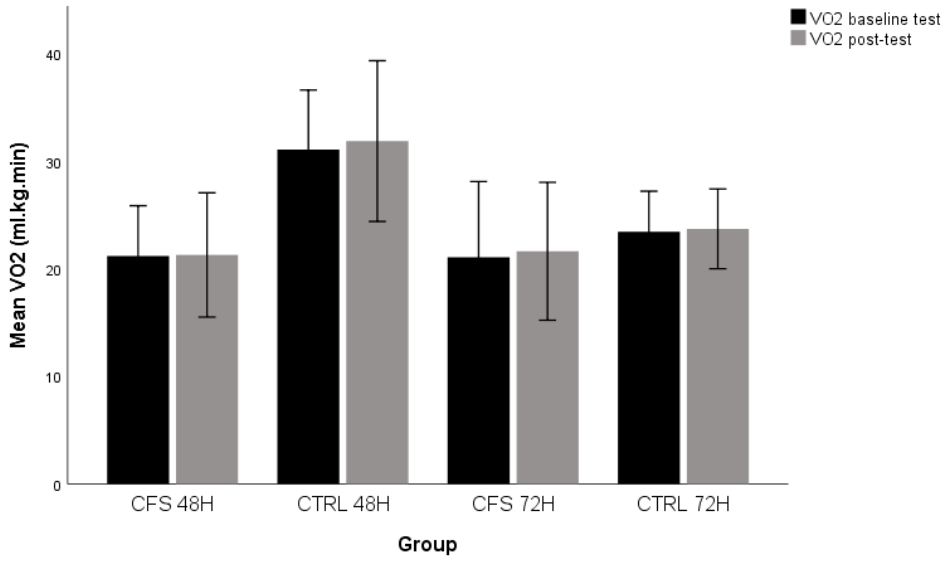

Figure 4 Mean VO_2 (ml.kg.min^{-1}) at the respiratory exchange ratio at the baseline test and post-test for all groups. Error bars represent the standard deviation.

Figure 4 illustrates that there was minimal changes in VO_2 between the baseline test and the post-test in all groups at RER (1.0).

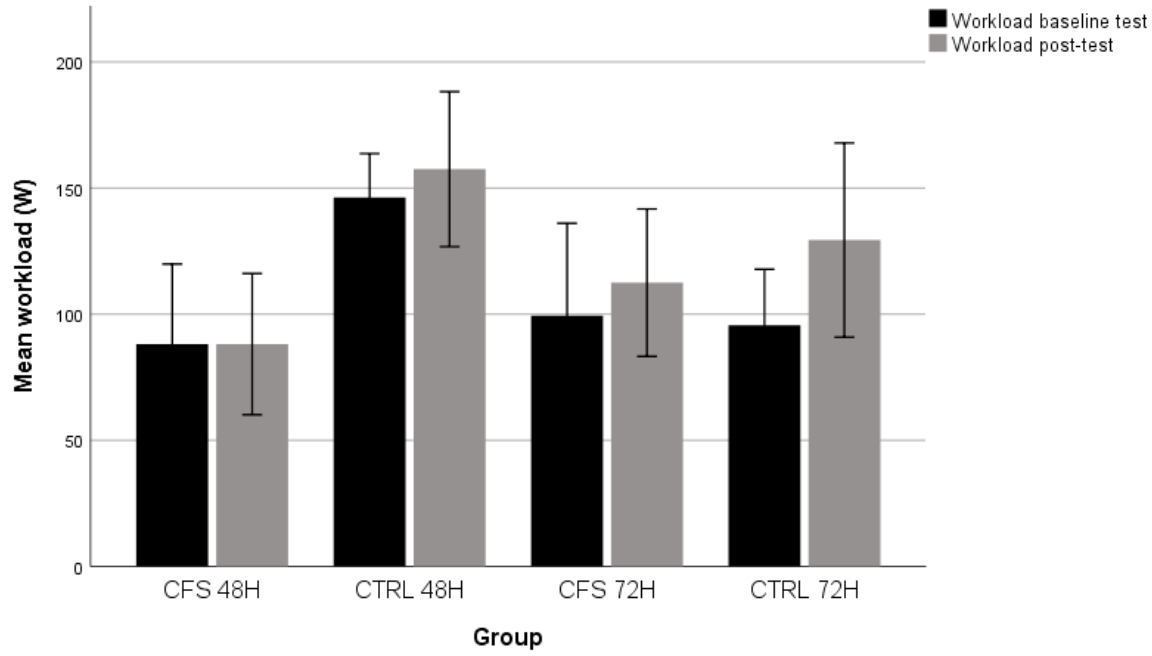

Figure 5 Mean workload (W) at the respiratory exchange ratio at the baseline test and post-test for all groups. Error bars represent the standard deviation.

Figure 5 illustrates the absence of change in workload (W) between baseline and post-test in the 48-hour group at RER (1.0). An increase in workload at 72-hours was evident in both the control group (p=0.013) and the ME/CFS group (p=0.087).

Table six shows additional submaximal data at the anaerobic threshold (AT), collected using the V-slope method (plotting VO_2 against CO_2 and determining the deviation point) (Schneider et al., 1993). Data collected at the AT is in contrast to that collected at RER of 1.0. This data shows significant differences between both ME/CFS groups and their controls of VO_2 at AT ($ml.kg.min^{-1}$) and workload (W) at AT, with ME/CFS participants reaching AT at reduced workload and VO_2 values in comparison to controls. This appears to be relative, as all groups reached AT at a similar percentage of their maximal capacity (50-65% $VO_{2\ max}$). Furthermore, for the 72-hour ME/CFS group a significant difference (p= <0.05) between days was noted. At the post-test, the 72-hour group reached AT significantly closer to $VO_{2\ max}$ in regards to the percentage of $VO_{2\ max}$ (7.1% later, p = 0.05) and workload (9.4 W higher, p = 0.049). There were no significant changes in any other group across days for AT.

Table 6 Mean (SD) submaximal physiological data at the anaerobic threshold at both baseline, 48-hours and 72-hours

	ME/CFS48h (n=8)	**CTRL48H (n=8)**	**P-value (grp)**	**ME/CFS72H (n=8)**	**CTRL72H (n=8)**	**P-value**
VO_2@ AT ($ml.kg.min^{-1}$)						
D1	14.8 (2.6)	22.5 (4.1)	***0.011****	13.5 (3.8)	20.1 (3.3)	***0.008****
D2	14.9 (2.8)	21.7 (4.5)	***0.019****	15.0 (2.9)	18.8 (3.4)	***0.02****
P-value *(days)*	*0.86*	*0.48*		*0.09*	*0.55*	
%VO_{2max} @ AT						
D1	60.1 (8.2)	55.4 (8.8)	*0.29*	55.9 (6.7)	58.9 (10.3)	*0.56*
D2	62.2 (7.6)	58.2 (5.8)	*0.31*	63.1 (11.9)	59.4 (8.01)	*0.33*
P-value *(days)*	*0.54*	*0.40*		***0.05****	*0.84*	
Workload @ AT (W)						
D1	54.4 (11.2)	71.2 (17.5)	***0.03****	54.4 (15.9)	73.1 (21.9)	***0.01****
D2	58.1 (12.5)	67.5 (13.9)	*0.28*	63.8 (19.2)	75.0 (27.8)	*0.30*
Sig (days)	*0.17*	*0.60*		***0.049****	*0.73*	

Key: D1 = baseline test; D2 = post-test (48 or 72 hours later); ME/CFS48H = ME/CFS 48-hour group; ME/CFS72H = ME/CFS 72-hour group; CTRL48H = Controls 48-hour group; CTRL72H = Controls 72-hour group; grp = differences between groups

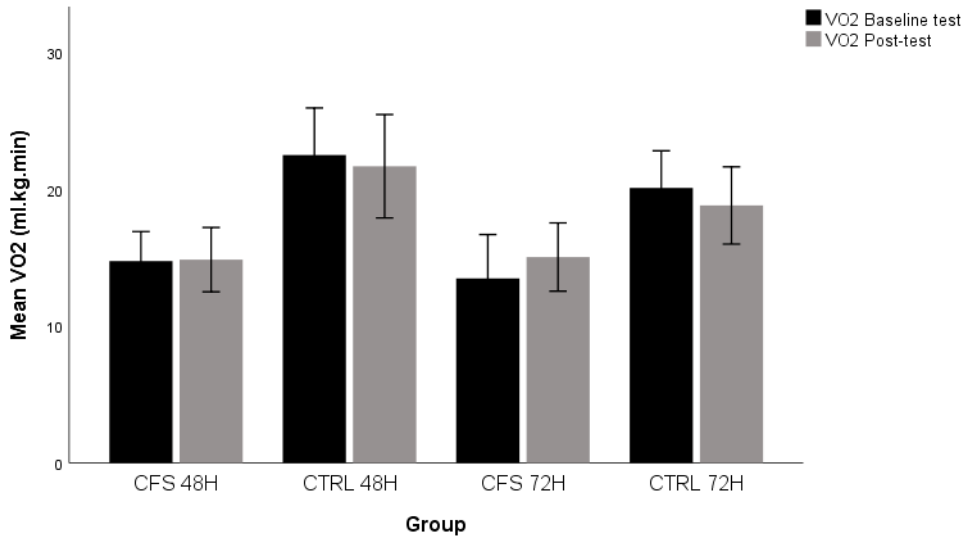

Figure 6 Mean VO_2 (ml.kg.min $^{-1}$) at the anaerobic threshold at the baseline test and post-test for all groups. Error bars represent the standard deviation.

Figure 6 illustrates measures of VO_2 (ml.kg.min^{-1}) at AT for ME/CFS participants and controls. It is evident that there were no significant changes between the baseline test and the post-test at either 48-hours or 72-hours.

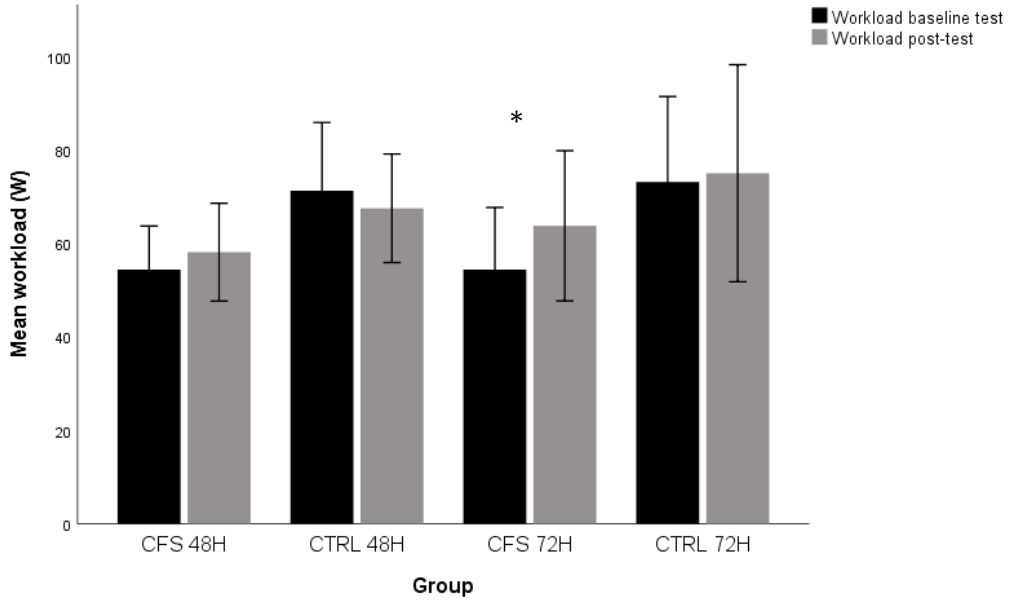

Figure 7 Mean workload (W) at the anaerobic threshold at the baseline test and post-test for all groups. Error bars represent the standard deviation.

Figure 7 illustrates changes in workload at AT; there was no significant differences at 48-hours. At 72-hours however, the ME/CFS group indicates a significant increase in workload.

5.3 Subjective Results

Results of the daily fatigue questionnaire are displayed in table 8. Participants recorded the number of days until they perceived to be fully recovered. Data shows a significant difference in recovery time between ME/CFS groups and their controls in both the 48-hour and 72-hour protocol ($p = 0.001$ $p = 0.013$ respectively). There is also a significant difference ($p = 0.047$) between the two ME/CFS groups; the 48-hour group took on average 10.7 days to recover after the second test, while on average, the 72-hour group had recovered after 5.5 days.

Table 7 Total days to recover by group

	ME/CFS 48H (n=7)	CTRL 48H (n=8)	ME/CFS 72H (n=8)	CTRL 72H (n=8)
Days to recover – mean (SD)	10.7 (4.79)	0.6 (1.06)	5.5 (4.31)	0.5 (0.53)

Participants were also asked a number of questions where a Likert scale of 1-10 was used to asses daily fatigue levels for 10-days following the exercise test; figure 8 includes mean answers to the question "How fatigued do you feel today on a scale of 1-10" in both CF/ME groups. It includes data from pre-exercise (3-days) and post exercise(10-days).

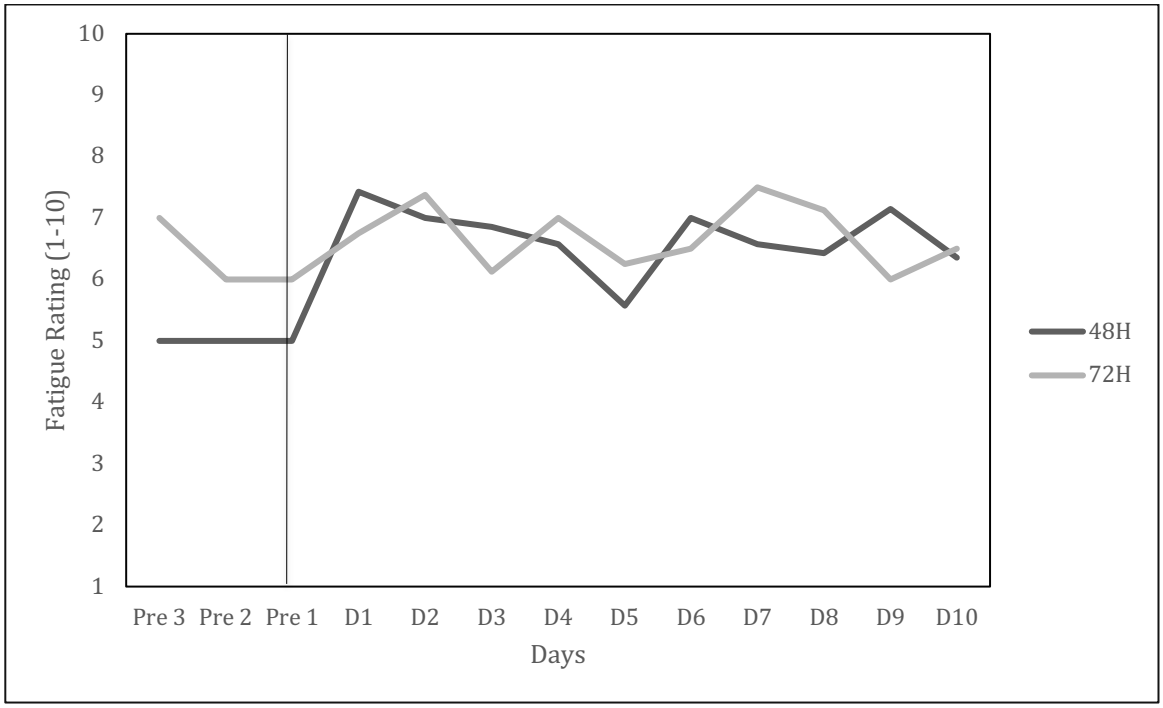

Figure 8 Mean subjective fatigue ratings 3-days prior to and 10-days following the exercise tests for all groups.

Figure 8 illustrates the absence of a clear identifiable trend. Results indicate that fatigue, both pre and post exercise, do not follow any specific pattern, with variations evident across the entire 13 days. There is a visible increase in fatigue in the 48-hour group after exercise due to a low baseline fatigue (5/10) and this appears to stay elevated post exercise to 10 days. In the 72-hour group however, there is no trend, with the graph only showing a spike in fatigue around the 7-day mark.

On close inspection of subjective recovery rates, there were 3 individuals within the 48-hour group who were recovered in 10-days and 4 individuals that took longer than 10-days to recover. When investigating these 2 groups independently, both groups had a very similar baseline fitness in regards to relative $VO_{2\ max}$ (26.5 vs. 26.1 ml.kg.min-^{1}). The group with the longer recovery did reach a higher mean workload (135 W compared to 100 W) and also had a higher "efficiency" at RER (5.2 vs. 3.8) than the group that recovered faster, this was evident for both the baseline test and the post-test. Within the 72-hour group there was only one person of 8 who took longer than 10-days to recover. Again, this individual's relative VO_2 was similar to the group, however at the post-test their workload and efficiency were notably higher than others from the group.

Table 8 Subjective data grouped based on total time to recover

	ME/CFS48H		ME/CFS72H	
	0-10 days (n = 3)	10-20 days (n = 4)	0-10 days (n = 7)	10-20 days (n = 1)
Relative VO_2 ($ml.kg.min^{-1}$)	26.45	26.17	23.96	21.92
Workload (W)	100	135	118	90
Efficiency (W/VO_2)	3.82	5.16	4.92	4.12
Test 2				
Relative VO_2 ($ml.kg.min^{-1}$)	25.82	23.25	23.63	24.88
Workload (W)	100	128	120	165
Efficiency (W/VO_2)	3.97	5.53	5.18	6.63

Key: ME/CFS48H = ME/CFS 48-hour; ME/CFS72H = ME/CFS 72-hour

CHAPTER SIX: DISCUSSION

6.1 Overview

The current study investigated the timeline of PEM in myalgic encephalomyelitis/chronic fatigue syndrome to determine whether a 48-hour or 72-hour repeated exercise protocol would provide new information regarding PEM. The study examined VO_2 ($ml.kg.min^{-1}$), workload (W), HR (bpm), RPE and RER at both maximal (VO_{2max}) and submaximal exercise (RER and AT). The aforementioned physiological values were compared between groups and across days. From the author's knowledge, this study was the first to utilise 48-hour and 72-hour repeated maximal exercise protocols to investigate PEM. As a secondary aim, subjective measures of PEM were collected to determine if a discernable pattern was evident.

6.2 Statement of Findings

Results of the study both support and counter the initial hypotheses. Results showed significant differences between ME/CFS participants and healthy individuals at maximal exercise (VO_{2max}) and submaximal exercise (RER and AT), with ME/CFS participants exhibiting reduced functional capacity in comparison to controls. The initial hypothesis predicted a further decline at both 48-hours and 72-hours. However, results indicated no further functional decline at either 48 or 72-hours after the initial exercise test. Physiological results showed no changes after 48-hours and an improvement in some measures after 72-hours in ME/CFS participants. The secondary hypothesis predicted high variation in subjective measures. Subjective results supported this hypothesis; no identifiable trend was observed in PEM with high variation across ME/CFS participants.

6.3 Maximal Outcomes

6.3.1. Between Group Outcomes

When comparing groups, maximal results in this study indicate significant differences in functional capacity between ME/CFS participants and healthy controls without a subsequent test, which is supported by previous research (Vermeulen & Vermeulen van Eck, 2014). At baseline and post-test, both ME/CFS groups had significantly lower VO_{2max} ($ml.kg.min^{-1}$) and maximal workload (W) compared to their controls. To-date, some studies, including that by Wallman et al. (2004), have identified no difference in baseline fitness levels in single tests, indicating that differences are only evident after the first test, which supports the use of repeated protocols (VanNess et al., 2007). Current findings suggest that a single test is sufficient to detect functional differences. Single test differences are likely due to the fitness of ME/CFS groups; both Vanness et al., (2007) and Hodges et al., (2017) observed no differences in fitness levels between ME/CFS and controls during a single test, differences were only evident post 24-hours, however both ME/CFS groups had a higher mean VO_{2max} than the current study.

Differences in functional capacity may be attributed to the inclusion criteria, or the variable nature of ME/CFS. Vaness et al., (2007) included a group of ME/CFS participants with the highest aerobic capacity (VO_{2max} of 26.2 $ml.kg.min^{-1}$) utilising what is deemed the least rigorous criteria, the Fukuda (1994). The current study utilised the ICC, which allows more impaired ME/CFS individuals to be included (Carruthers et al., 2011). It is also important to note that abnormalities in functional capacity are evident in a number of conditions, although these values are significant, they do not differentiate ME/CFS from other conditions that also experience deconditioning (Van Oosterwijck et al., 2010). Hodges et al., (2017) reported that the MS group in their study was notably deconditioned during a single test, however after 24-hours the MS group improved in numerous measures, further highlighting the need for a repeated protocol.

6.3.2 Between Days Outcomes

Maximal results between days indicate very few changes at both 48-hours and 72-hours; at 48-hours the ME/CFS group were able to achieve a similar workload to the

baseline test (p = 0.685) and the 72-hour group saw only a minor increase in achievable workload (p = 0.285). Oxygen consumption (VO_2) also remained similar across tests for all groups. These findings do not support the hypothesis, which predicted a further decline of PEM at 48 and 72-hours. The majority of 24-hour studies (Vanness et al., 2007; Vermeulen et al., 2010; Keller et al., 2014; Hodges et al., 2017), observe a decrease in VO_{2max} after 24-hours. Vaness et al., (2007) identified the most significant decline (-5.76 ml.kg.min^{-1}). The only study to identify an increase in VO_{2max} was Hodges et al., (2017) and this increase was only minor (+1.32 ml.kg.min^{-1}) with a concomitant significant decrease in workload (-9 W).

As the first study to utilise a repeated exercise protocol beyond 24-hours, there is little opportunity for direct physiological comparison. However, subjective data to-date observing the timeline of PEM remains equivocal. Lindheimer et al., (2017), reported no change in fatigue at 48-hours, but at 72-hours fatigue significantly increased and motivation was reduced (Lindheimer et al., 2017). In contrast, Bazelmans et al., (2005) identified that the severity of PEM was heightened at 48-hours and returned to baseline by 72-hours. In support of current findings, Keech et al., (2015), suggests that the severity of PEM peaks immediately following exercise (>24-hours) and returns baseline by approximately 72-hours. The conflicting results from the subjective studies are likely due to variations in methodology used and personal variations in how participants scale their "fatigue". The current study provides some clear objective information, which more closely details the fatigue response from a physiological perspective. More research is required, which includes both objective and subjective measures of fatigue.

6.4 Submaximal (RER & AT) Outcomes

6.4.1 Between Group Outcomes

When comparing groups at RER, differences in aerobic capacity were only evident within the 48-hour group – ME/CFS participants attained RER at a significantly lower workload and VO_2 than their controls. The 72-hour groups did not display physiological differences at RER, however, there was a significant difference in RPE indicating that ME/CFS participants felt that the load was harder than the controls, despite it being similar (e.g. 99 W vs. 96 W). At AT, differences in submaximal capacity

became more evident, with significant differences observed between both ME/CFS groups and their control groups at AT, in regards to both VO_2 and workload. This further supports the notion that AT may be a more suitable measure to utilise for compromised populations (Wasserman et al., 1994; Williamson et al., 2012). Respiratory exchange ratio has been verified for use on individuals with high aerobic capacity (Wasserman et al., 1994), however previous research suggests that validity increases with intensity and therefore for deconditioned individuals, the AT is more reliable (Williamson et al., 2012).

6.4.2 Between Days Outcomes

There were no significant changes across days within the 48-hour protocol, with both groups reaching RER at a similar workload after 48-hours. This finding is in contrast to the hypothesis, predicting a further decline at 48-hours. Within the 72-hour protocol, both groups attained RER at a later point during the post-test indicating improved efficiency (ME/CFS = + 13.12 W, CTRL = +33.75 W); however, although the ME/CFS group did improve, only the increase within the control group was significant ($p= 0.013$). This improvement does not support the current hypothesis, predicting that PEM would still be evident at 72-hours. In fact, results suggest that functionality may improve 72-hours following an exercise bout. Data collected at AT further emphasises these findings. At AT, improvements in workload and percentage of VO_{2max} were of significance for the 72-hour ME/CFS group only; further suggesting improved submaximal functionality 72-hours after the initial exercise test. It is important to note that the 72-hour group did have four males, compared to only one within the 48-hour group, which may have influenced results.

All four groups experienced an increase in VO_2 ($ml.kg.min^{-1}$) at the post-test at RER, however no increases were significant. These results differ from the responses observed at 24-hours. Repeated 24-hour studies consistently identify a decline in functionality at RER in both workload and VO_2 (Hodges et al., 2017), and researchers using AT have also consistently observed a decline (Keller et al., 2014; Snell et al., 2013; VanNess et al., 2007; Vermeulen et al., 2010). The present results suggest that following a lengthened recovery period, this decline is no longer evident. Furthermore, current findings indicate a potential improvement in submaximal functionality 72-hours after

exercise in ME/CFS. However, in regards to diagnosis 48-hour and 72-hour protocols may not be ideal in comparison to 24-hour protocols which consistently provide functional evidence of PEM. Results of the current study do not provide objective evidence of PEM at 48 and 72-hours. However, results do potentially offer some recommendations for future studies wanting to assess differing treatment protocols. If functionality does improve across 72-hours, then perhaps graded exercise therapy utilising this approach, may elicit positive improvements in function over time. Additional research at 72-hours is required to further explore, and confirm this theory.

6.5 Practical Implications: Diagnosis, Treatment and Ongoing Research

When assessing physiological results collectively, neither the 48-hour protocol nor the 72-hour protocol highlights PEM as effectively as 24-hour protocols have to date. It appears that a decline in workload at submaximal exercise (RER and AT) is of particular interest with the most significant and consistent observations being reported (Hodges et al., 2017; Keller et al., 2014; Snell et al., 2013). The current study did not observe this same decline at 48 or 72-hours, suggesting that PEM was no longer evident or at least visible on a physiological level at these intervals. Similar to 24-hour studies to-date (Vermeulen et al., 2010;Snell et al., 2013; Keller et al., 2014; Hodges et al., 2017), the current study observed more significant changes across days at RER/AT compared to maximal exercise, supporting its use as an observational point. However, these changes did not indicate worsening PEM and instead support its decline post-24-hours. As the first objective study beyond 24-hours, more research is needed to confirm and/or challenge these findings. Using the same participants would provide an appropriate comparison of 24, 48 and 72-hour protocols to confirm the present results.

An interesting finding of this study was the difference in observations at AT and RER; AT occurred earlier during exercise in the current study and highlights the functional improvements in the 72-hour ME/CFS group, these differences were still evident, but less so at RER. Furthermore, differences between ME/CFS participants and healthy controls were more evident at AT compared to RER. Previous studies have included one or the other, warranting caution when making comparisons between studies (Hodges et al., 2017; VanNess et al., 2007). Consistency in submaximal measures

utilised and presented is an aspect researchers should consider. The current study suggests that AT may be a better measure for ME/CFS individuals.

Physiological findings of the current study provide further information in regards to the timeline of PEM, for diagnosis and treatment purposes. The observed improvement in submaximal functionality at 72-hours suggests that an adequate recovery level was attained for ME/CFS individuals and subsequent exercise could be performed without further side-effects. Current protocols utilising graded exercise therapy predominantly involve exercise bouts only once a week or once a fortnight; perhaps with more regular exercise, results of these trials could be enhanced (White et al., 2011).

6.6 Subjective Outcomes

The subjective portion of this study was included to offer more information on the PEM timeline and whether discernable trends exist. In line with previous research, subjective feedback found that on average, controls took less than one day to recover after the second exercise test; however ME/CFS groups took significantly longer. Following the 48-hour protocol, participants took on average 11 days and following the 72-hour protocol, participants took on average 5.5 days to feel recovered. This highlights that although ME/CFS patients could perform similarly at both exercise tests, this physical capability occurs alongside lengthy subjective recovery. The 48-hour protocol elicited a significantly pro-longed period of exacerbated fatigue, compared to the 72-hour group. It could be proposed that by allowing 2-days between exercise bouts within the 72-hour protocol, participants were able to reduce the extent of their PEM.

There appears to be weaknesses in assessing means of the entire group where ME/CFS is concerned. Graphed data shows fatigue levels across days vary greatly; it is evident that ME/CFS participants respond differently to subjective measures of fatigue. Results support the hypothesis, that no discernable trends of subjective fatigue were evident during PEM. Subjective research by Keech et al., (2015) identified frequent outliers when investigating a ME/CFS population. Additionally, Davenport et al., (2011) identified high variation between ME/CFS participants, with some recovered by 7-days, and others still experiencing symptom exacerbation at 7-days post exercise.

When analysing subgroups from the current study, those participants who took longer (10+ days) to recover, did so after working at a higher workload despite a similar VO_2, to those who recovered faster (within 10-days). The relationship between higher efficiency and prolonged recovery is interesting, as increased efficiency is considered a positive adaption to exertion (Prieur et al., 2005). In this case it appears that an improved efficiency is related to a longer recovery period.

6.7 Limitations

When investigating ME/CFS as a population there is a large variation between individuals and their fatigue on any given day, as well as their overall impairment. Therefore, it is often difficult to determine whether the ME/CFS sample accurately represents its population. Effort was made to reduce these limitations by implementing a consistent recruitment tool and asking that participants partake only in usual activity outside of testing times. I.e. nothing that would further exacerbate fatigue and other symptoms. Furthermore, through the use of the mobile laboratory, participant travel was reduced.

6.8 Recommendations for future research

Additional research is required to investigate whether repeated exercise protocols at 48-hours and 72-hours support or challenge the findings of the current study. A study investigating all three timelines (24-hour, 48-hour and 72-hour) with a consistently sourced group of ME/CFS participants would provide consensus for the best diagnostic protocol.

Furthermore, based on the improvements observed at 72-hours, treatment studies involving more frequent exercise may be warranted to investigate whether this may improve functionality over time more so than current treatment protocols, involving less frequent exercise.

CHAPTER SEVEN: CONCLUSIONS

The purpose of this study was to determine the timeline of PEM in ME/CFS, to discern the optimal time point for diagnostic purposes and secondly, to determine whether subjective fatigue follows a discernable trend post-exercise.

This study identified no symptom exacerbation at a functional level at 48 or 72 hours after the first exercise test. The physiological results of this study provide new information regarding a potential improvement in submaximal efficiency 72-hour after an exercise bout in ME/CFS patients, due to an increase in both workload and percentage of VO_{2max} at key submaximal points during the second test (RER and AT). As a practical implication, these findings further support the use of 24-hour repeated protocols in ME/CFS diagnosis, opposed to 48 and 72-hour protocols. Subjective results of the study revealed no obvious trend in subjective fatigue following maximal exertion, with high variation in participant recovery rates. A relationship was observed between submaximal efficiency and length of recovery, but more research is needed to understand this.

CHAPTER EIGHT: REFERENCES

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CHAPTER NINE: APPENDICIES

9.1. Participant information sheet and consent form

Participant Information Sheet

Your letterhead

Study title:	EXERCISE AND CHRONIC FATIGUE SYNDROME		
Locality:	**Massey University, Palmerston North**		
Lead investigator:	**Dr Lynette Hodges**	Contact phone number:	**063569099**

You are invited to take part in a study on exercise. Whether or not you take part is your choice. If you don't want to take part, you don't have to give a reason, and it won't affect the care you receive. If you do want to take part now, but change your mind later, you can pull out of the study at any time.

This Participant Information Sheet will help you decide if you'd like to take part. It sets out why we are doing the study, what your participation would involve, what the benefits and risks to you might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. You do not have to decide today whether or not you will participate in this study. Before you decide you may want to talk about the study with other people, such as family, whānau, friends, or healthcare providers. Feel free to do this.

If you agree to take part in this study, you will be asked to sign the Consent Form on the last page of this document. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep.

This document is 6 pages long, including the Consent Form. Please make sure you have read and understood all the pages.

WHAT IS THE PURPOSE OF THE STUDY?

The purpose of the study is to provide physiological information regarding the fatigue response following repeated exercise in those with CFS, compared to healthy controls, at 48 and 72 hours following exercise. Based on previous findings, it looks to identify potential CFS subgroups in regards to the timing of the fatigue response.

The study is being carried out by Dr Lynette Hodges at Massey University, from the School of Sport and Exercise. Lynette can be contacted by telephone on 063569099 or by e-mail: L.d.hodges@massey.ac.nz and would be happy to answer any questions you may have.

WHAT WILL MY PARTICIPATION IN THE STUDY INVOLVE?

You are invited to participate in the study because you have been diagnosed with Chronic Fatigue Syndrome or are an age-matched control that is healthy and free from disease. Both male and females are invited to participate and age of participants must fall within 18 years and 65 years.

All participants will be asked to visit the mobile Human Performance Lab, at 56 Christopher Street, Tauranga South on two occasions, an initial testing session and a second session either 48 or 72 hours later. During the first visit, you will have the following resting measures taken:

* Height and weight
* Blood pressure
* Arterial stiffness measured through ultrasound of the carotid artery.
* 4 neuropsychological computer tests (Stroop, Trail, Substitution and Choice tests). This will give us information about how quickly and correctly you can process information.

Individuals will then complete an incremental cycle ergometer exercise test to volitional exhaustion. During the test, you will exercise at progressively harder intensities until you cannot continue. This will tell us about your heart and lungs. During the exercise test we will monitor your heart rate, blood pressure, and your rating of perceived exertion (how you are feeling). You will also be asked to complete an exercise recovery questionnaire.

You will then need to return to the lab either 42 or 78 hours later, where each test will be repeated. Testing on each occasion should take no more than an hour and a half of your time. Following the completion of the exercise tests, you will complete a daily diary of fatigue each day for 10-days. The purpose of the questionnaires are so that we can quantify and clarify different types of fatigue and also how long it takes for each group to fully recover from the exercise testing. Health information relating to your condition will be collected and recorded in the first visit.

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF THIS STUDY?

The procedures involved in this study are of low risk. Nevertheless, as in any invasive procedures there are small risks and some discomfort may be experienced

Exercise testing

There is the possibility of certain changes occurring during and after intense exercise. These may include; abnormal blood pressure, dizziness, fainting, abnormal heart rate or rhythm, muscular soreness, sprains, strains and fractures, nausea and vomiting, mild to severe breathlessness, and in rare circumstances heart attack, stroke or even death. Every effort is made to minimise these risks by careful evaluation of the information supplied by you regarding the state of your health and current fitness level and by careful observations of heart rate, blood pressure.

There is the possibility that you may suffer from additional fatigue for a period of up to four weeks following the exercise testing.

Benefits

The results obtained in this study will be used to develop a method for evaluating whether an individual has CFS and how this affects their functional ability. You will be provided with your individual results for peak oxygen consumption, heart rate levels as well as those levels at your anaerobic threshold. It is anticipated that this research will provide new information about the time course of fatigue following exercise, which will be valuable in creating solutions for exercise prescription in the future. If exercise testing can show that an individuals have CFS, this testing method of diagnosis would save both time and money for the medical practitioners and would also provide a piece in the jigsaw for individuals with chronic fatigue syndrome and give them the recognition they deserve.

WHO PAYS FOR THE STUDY?

All costs incurred by the study will be funded by Massey University. Participants will not incur any costs. Any parking costs associated with the study will be reimbursed.

WHAT IF SOMETHING GOES WRONG?

If you were injured in this study, which is unlikely, you may be eligible for compensation from ACC just as you would be if you were injured in an accident at work or at home. You will have to lodge a claim with ACC, which may take some time to assess. If your claim is accepted, you will receive funding to assist in your recovery.

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

WHAT ARE MY RIGHTS?

- Participation in the study is voluntary. You are free to decline to participate, or to withdraw from the research at any practicable time, without experiencing any disadvantage.
- You have the right to access information about yourself, collected as part of the study
- Participants will be informed of any new information about adverse or beneficial effects related to the study that becomes available during the study that may have an impact on their health
- All information collected within the study will be kept confidential. Health records and personal information will only be available to the researchers involved in the study.

WHAT HAPPENS AFTER THE STUDY OR IF I CHANGE MY MIND?

Following this study it is anticipated that there will be an intervention study aimed at investigating the effect of vibration training on biomarkers of fatigue, which will be at no cost. Participants from the current study may be contacted, but would need to complete a further participant consent form to take part in this study.

Study data will be stored for in a locked filing cabinet and a password protected computer for 10 years. Following this all information will be destroyed by the researcher via a confidentiality waste refuse bin.
The findings of the study will be communicated to the patients, on completion of the study via a report which will be sent to each patient and a presentation which will be completed at the local groups for MS and CFS within 6 months of the cessation of the study.

WHO DO I CONTACT FOR MORE INFORMATION OR IF I HAVE CONCERNS?

If you have any questions, concerns or complaints about the study at any stage, you can contact: Lynette Hodges, Lecturer in Sport and Exercise, Phone: 063569099 or E-mail: L.d.hodges@massey.ac.nz.

If you want to talk to someone who isn't involved with the study, you can contact an independent health and disability advocate on:
Phone: 0800 555 050
Fax: 0800 2 SUPPORT (0800 2787 7678)
Email: advocacy@hdc.org.nz

For Maori health support please contact :
Bevan Erueti: Maori Cultural Advisor
Phone: 06 356 9099 Ext 83087
E-mail: B.Erueti@massey.ac.nz

You can also contact the health and disability ethics committee (HDEC) that approved this study on:
Phone: 0800 4 ETHICS Email: hdecs@moh.govt.nz

MASSEY UNIVERSITY
School of Sport and Exercise
Private Bag 11 222
Palmerston North
New Zealand
Telephone: 64 6 350 4336
Facsimile: 64 6 350 5657

Consent Form

If you need an INTERPRETER, please tell us.

Please tick to indicate your consent to the following

I have read, or have had read to me in my first language, and I understand the Participant Information Sheet.	Yes ☐	No ☐
I have been given sufficient time to consider whether or not to participate in this study.	Yes ☐	No ☐
I have had the opportunity to use a legal representative, whanau/ family support or a friend to help me ask questions and understand the study.	Yes ☐	No ☐
I am satisfied with the answers I have been given regarding the study and I have a copy of this consent form and information sheet.	Yes ☐	No ☐
I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without this affecting my medical care.	Yes ☐	No ☐
I consent to the research staff collecting and processing my information, including information about my health.	Yes ☐	No ☐
If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw may continue to be processed.	Yes ☐	No ☐
I consent to my GP or current provider being informed about my participation in the study and of any significant abnormal results obtained during the study.	Yes ☐	No ☐
I understand that there may be risks associated with the treatment.	Yes ☐	No ☐

I agree to an approved auditor appointed by the New Zealand Health and Disability Ethic Committees, or any relevant regulatory authority or their approved representative reviewing my relevant medical records for the sole purpose of checking the accuracy of the information recorded for the study.	Yes ☐	No ☐
I understand that my participation in this study is confidential and that no material, which could identify me personally, will be used in any reports on this study.	Yes ☐	No ☐
I understand the compensation provisions in case of injury during the study.	Yes ☐	No ☐
I know who to contact if I have any questions about the study in general.	Yes ☐	No ☐
I understand my responsibilities as a study participant.	Yes ☐	No ☐
I wish to receive a summary of the results from the study.	Yes ☐	No ☐

Declaration by participant:
I hereby consent to take part in this study.

Participant's name: _____

Signature: _____ Date: _____

Declaration by member of research team:

I have given a verbal explanation of the research project to the participant, and have answered the participant's questions about it.

I believe that the participant understands the study and has given informed consent to participate.

Researcher's name: _____

Signature: _____ Date: _____

9.2 Daily diary of fatigue
(7-days given prior, 10-days given post)

ID Code: **Date:**

Please answer the following questions thinking about how your <u>fatigue</u> has been <u>today.</u>

Circle one response for each question

1. How Severe was your **fatigue** today?
   0 = I did not experience fatigue today **10 = Extremely severe**

   0 1 2 3 4 5 6 7 8 9 10

2. How **worn out** did you feel today?
   0 = Not at all worn out **10 = Extremely** worn out

   0 1 2 3 4 5 6 7 8 9 10

3. How **easily** did you **get tired** today?
   0 = I did not get tired easily today **10 =** I got tired **extremely easily** today

   0 1 2 3 4 5 6 7 8 9 10

4. How **exhausted** did you feel today?
   0 = Not at all exhausted **10 = extremely** exhausted

   0 1 2 3 4 5 6 7 8 9 10

5. How **tired** did your **body** feel today?
   0 = Not at all tired **10 = Extremely** tired

   0 1 2 3 4 5 6 7 8 9 10

9.3 Exercise Recovery Questions

MASSEY UNIVERSITY
School of Sport and Exercise
Private Bag 11 222
Palmerston North
New Zealand
Telephone: 64 6 350 4336
Facsimile: 64 6 350 5657

ID:_____ Date of Exercise Test:_____

1. How did you feel following the first exercise test?
   _____
   _____
   _____

2. Describe how you felt the day after the first exercise test.
   _____
   _____
   _____

3. How did you feel following the second exercise test?
   _____
   _____
   _____

4. Describe how you felt the day after the second exercise test.
   _____
   _____
   _____

5. How long did it take you to recover from the exercise tests? E.g. How many hours or days?
   _____

6. Describe symptoms, if any, experienced after the exercise test.
   _____
   _____
   _____