The physiological and cognitive effects of a repeated 5-minute exercise challenge on individuals with ME/CFS.

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ABSTRACT

PURPOSE: Recently exercise prescription has been cast into doubt surrounding the effectiveness of exercise as a treatment for those with ME/CFS. This study investigated the effects of a repeated 5 minute exercise challenge on the physiological and cognitive markers in those with ME/CFS. With the intention of being able to provide recommendations regarding safe and beneficial exercise to aid with the treatment and management of symptoms experienced by those with ME/CFS.

METHODS: Eleven participants with ME/CFS completed three testing sessions. On the first visit, each participant completed a battery of neuropsychological tests, resting and standing Heart Rate Variability (HRV), as well as an incremental, maximal cycle test. On the second and third visit, participants completed the same battery of neuropsychological and HRV tests, but also included a steady state exercise challenge at Anaerobic Threshold (AT), determined from the initial maximal exercise test. The second and third visit were separated by 24 hours.

RESULTS: From the maximal exercise test, a low mean $\dot{V}O_2$ (23.36 ml.kg.min) and a high blood pressure (BP) (169/97mmHg), relative to mean heart rate (HR) (155bpm) and workload (131W) were found. HR response was low relative to the exercise intensity, with only one participant reaching their precalculated age predicted max heart rate (APMHR). From the repeated 5-minute exercise challenge, there was a reduction in $\dot{V}O_2$ (18.7ml.kg.min to 16.01ml.kg.min). BP followed a similar trend to the maximal exercise test, where mean SBP and DBP were high relative to HR and workload. From analysis of $\dot{V}O_2$, Respiratory Exchange Ratio (RER) and Rating of Perceived Exertion (RPE), individuals were exercising at Anaerobic Threshold (AT), yet 6 of the 11 participants had an HR and BP response equivalent to greater than 84% of their max. The repeated exercise challenge did not reduce cognition. Results also demonstrated that the exercise challenge reduced the recovery from a mean of 9.18 days with the CPET to 5.23 days from the repeated exercise challenge.

CONCLUSIONS: This study identified new information surrounding the BP and HR response to exercise, experienced by those with ME/CFS. The information detailed provides a good opportunity for future research, particularly aiming to provide further understanding of why those with ME/CFS have this physiological response to exercise. The results also provided details about how APMHR is not necessarily a useful prescription tool for those with ME/CFS due to the great variation between individuals.

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A

ANS	Autonomic Nervous System
APMHR	Age Predicted Max Heart Rate
AT	Anaerobic Threshold
AVNN	Average of Intervals Between Successive Heartbeats

B

BMI	Body Mass Index
Bpm	Beats Per Minute
BP	Blood Pressure

C

Cm	Centimetres
CFS	Chronic Fatigue Syndrome
CCC	Canadian Consensus Criteria
CO_2	Carbon Dioxide Production
CPET	Cardiopulmonary Exercise Test

D

DBP	Diastolic Blood Pressure

G

GET	Graded Exercise Therapy

H

HRV	Heart Rate Variability
HR	Heart Rate
HRmax	Heart Rate Max

I

ICC	International Consensus Criteria

K

Kg	Kilograms

L

LF	Low Frequency Band

M

M	Metres
ME	Myalgic Encephalomyelitis
$ml.kg.min^{-1}$	Millilitres per kg per Minute
mmHg	Millimetres of Mercury

P

PEM	Post Exertional Malaise
pNN50	Proportion of Normal-to-Normal Heartbeat Intervals Greater than 50ms

R

RPE	Rating of Perceived Exertion
RER	Respiratory Exchange Ratio
RHR	Resting Heart Rate
rMSSD	Root Mean Square of Successive Differences in Heartbeats
RPM	Revolutions per Minute

S

SBP	Systolic Blood Pressure
SD	Standard Deviation
SDNN	Standard Deviation of Intervals Between Successive Heartbeats

V

$\dot{V}O_2$	Oxygen Consumption

W

W	Watts

CHAPTER ONE: INTRODUCTION

Myalgic Encephalomyelitis (ME) is a debilitating clinical condition that is predominantly characterised by unexplained but persistent fatigue, accompanied by a variety of other symptoms related to immunological, cognitive, endocrinological and/or autonomic dysfunctions (Cortes-Rivera et al., 2019). The name Myalgic Encephalomyelitis was first included in the World Health Organisation's International Classification of Diseases in the 1960's (Hooper, 2007). Following this, Chronic Fatigue Syndrome (CFS) was initialised and defined in the 1980's (Clayton, 2015). The most recent but perhaps not common name for this debilitating condition is Systemic Exertion Intolerance Disorder, which was introduced with the idea of reducing the perception derived from the inclusion of the word 'fatigue' and rather highlighting other core symptoms of this systemic physical illness instead of just fatigue (Lim and Son, 2020).

Within the 4.8 million population of New Zealand, an estimated 20,000 individuals are said to be diagnosed with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) (ANZMES, 2017). The primary symptom of ME/CFS is considered but not limited to be debilitating fatigue, reducing activity to less than 50% of the individual's premorbid activity, that has been experienced for at least 6 months (Wright and Beverley, 1998). Although ME/CFS is considered a debilitating condition, medical practitioners find diagnosis and management/treatment challenging. Healthcare and social services delivery to ME/CFS patients in New Zealand is fragmented, or non-existent due to the skepticism despite the compelling international evidence. Typically, there has not been a single lead care coordinator among medical or allied health specialties in New Zealand. It has recently been proposed that ME/CFS is a condition that may occur as a result of a life event that puts the body under excess stress (physically and/or emotionally), resulting in the inability to recover from this event (Moss-Morris, Deary and Castell, 2013). However, research is ongoing relating to this and other potential causes of ME/CFS.

The primary method for diagnosing ME/CFS involves a subjective symptom-based questionnaire, by which responses are marked against a set of criteria (Haney et al., 2015). There are many questions surrounding the current criteria due to the misinformation often interpreted by health professionals, and the lack of understanding surrounding the aetiology of ME/CFS (Baker and Shaw, 2007). The primary subjective criteria are identified as the Fukuda

Criteria (1994), the Canadian Consensus Criteria (CCC) (2003) and the International Consensus Criteria (ICC) (2011) (Sunnquist et al., 2017). Twisk (2014), suggest that due to the current lack of statistical and scientific validation surrounding the diagnostic criteria, there is no one method advocated to be the "gold standard" for diagnosing ME/CFS. Although, Yancey and Thomas (2012), have suggested that the utilised subjective criteria provides a wide consensus on the symptoms experienced by individuals, to provide an evidence-based diagnosis of ME/CFS. Beyond these subjective measures, there is also a significant objective marker that is exploited in diagnostic criteria and is considered a "hallmark symptom" for ME/CFS, with this being Post Exertional Malaise (PEM) (Holtzman et al., 2019). These criteria are used within this study to determine eligibility for participation.

The relationship between exercise and ME/CFS is a long-standing investigation. Commonly it has been suggested that even minor physical exertion causes a drastic exacerbation of ME/CFS symptoms (Cook et al., 2013). Many disparities have been identified in current research with some scholarly articles suggesting there is a positive relationship between exercise and ME/CFS symptoms, particularly surrounding management and prevention of disease (Larun et al., 2017; Matheson et al., 2011). With others suggesting incorrect exercise prescription is leading to increased amounts of PEM, reducing quality of life in those with ME/CFS (Cook et al., 2013). Due to the current lack of understanding surrounding exercise prescription, particularly regarding how much exercise is acceptable for those with ME/CFS, individuals are experiencing great amounts of PEM, induced by excessive levels of exacerbation which in turn is resulting in notable functional impairment beyond what is a normal response to exercise (Institute of Medicine, 2015). Fulcher and White, (1998), have identified some benefits of exercise to those with ME/CFS, with these including improvements in strength, endurance and symptoms. However, research into the relationship between exercise and ME/CFS is still in its infancy with many questions remaining, particularly surrounding beneficial intensities and frequencies of exercise, thus making this research study a significant step in understanding the relationship of how exercise affects the physiological system of those with ME/CFS.

This thesis initially provides an extensive literature review (Chapter Two), providing a comprehensive insight into the background of ME/CFS, along with an examination of aetiology, symptomology, current diagnostic measures, PEM, the current state of play in the relationship between ME/CFS and heart rate variability (HRV) and cognitive functioning. It also highlights the impact of exercise on those with ME/CFS and current ideas surrounding treatment strategies. Chapter Three, has detailed aims and objectives of the main research

study, moving on to Chapter Four where the methods are addressed. The results are presented in Chapter Five then discussed with reference to potential limitations and possible recommendations for future research in Chapter Six. Finally, Chapter Seven will draw all information gathered together and will conclude what has been found and discuss an appropriate path forward.

CHAPTER TWO: LITERATURE REVIEW

2.1 ME/CFS Background

Myalgic Encephalomyelitis (ME) also known as Chronic Fatigue Syndrome (CFS) is a neurological condition that is estimated to affect 20,000-25,000 individuals, within New Zealand (Hodges, Nielsen and Baken, 2018). Females are two to three times more likely to be diagnosed with ME/CFS than males (Chu et al., 2019). The distribution ratio of females to males being 3:1 (Cortes-Rivera et al., 2019), with its' onset typically becoming prominent at two age peaks, the first at 10–19 years of age and secondly at 30–39 years of age (Collin et al., 2015). However, it is more widely acknowledged that it affects adults with a peak age of onset between 20 and 45 years of age (Cortes-Rivera et al., 2019). It is defined by Hatziagelaki et al., (2018), as a complicated disease that is mainly characterised by debilitating fatigue that is present for 6 months or longer, which can have a hindering effect on physical activity levels reducing daily activity by at least, if not more, than 50% (Hudson 2014), From this literature review more details surrounding the aetiology and symptomology will be highlighted, along with information regarding the current diagnostic measures. PEM will be discussed as well as an in depth analysis of the relationship between ME/CFS and HRV, and cognitive functioning. Along with aspects of the relationship between ME/CFS and exercise being highlighted, to provide a basis of understanding for this report. Finally, current ideas surrounding treatment options for ME/CFS will be provided.

2.2 Aetiology and Symptomology

The aetiology of chronic conditions are typically a well understood aspect, unfortunately this is not the case with ME/CFS. The pathogenic mechanisms of ME/CFS are not completely understood, however, several hypotheses as to the cause of ME/CFS have been established. These predominantly surround areas of the central nervous system such as neurological, immunological and/or endocrinological dysfunction (Fernandez et al., 2009). There is not enough current evidence that can link one particular factor to the underlying cause of ME/CFS, however many triggers are suggested. The aetiology behind ME/CFS seems to be a pool of many factors characterised primarily by somatic and neuropsychiatric symptoms (Shafran, 1991; Farrar, Locke and Kantrowitz, 1995). Thus being said, it is likely that ME/CFS is a chronic condition, that is made up of many smaller immunological aberrations that are frequent among many, however, significance of the aberrations is still highly uncertain (Shafran, 1991).

Although the aetiology of ME/CFS still has grey areas, some trends have been highlighted through the examination of current diagnostic measures. Research completed by Chu et al., (2019) suggests that from a pool of 150 individuals with ME/CFS that completed the Fukuda (1994) CFS criteria survey, the common peri-onset events reported were infection-related episodes, and the inability to recover from these (64%), exposure to environmental toxins (20%) and stressful incidents (39%). The most common symptoms expressed by these 150 participants were said to be fatigue, unrefreshing sleep, exertion-related sickness, post-exertional malaise, and consistent flu-like symptoms (Chu et al., 2019). This can be backed up by evidence by Fernandez et al., (2009), that suggests the most common symptoms of ME/CFS are deemed to be decreased immunological functioning, fatigue, fever or intermittent dysthermia, generalised muscular pain, lingering sore throats, persistent headaches, and/or tender cervical or axillary lymph nodes. These symptoms along with the diagnosis of ME/CFS tend to have profound implications on quality of life and daily functioning for those living with the condition.

2.3 Current Diagnostic Measures

Current research suggests that despite the life changing affect ME/CFS has on individuals and their families, there are currently no diagnostic tools beyond symptom recognition (Robinson, et al., 2019). Evidence suggested by Hudson, (2014), states that to determine ME/CFS, fatigue levels must become so severe that it forces a 50% reduction in daily activities such as occupation, education, social or personal activities. This definition can be backed up by Carruthers et al., (2011), that suggest ME/CFS is a complex disease that incorporates profound dysregulation of the central nervous system and the immune system, along with dysfunction of cellular energy metabolism and potential cardiovascular abnormalities. Research in more recent years has discovered that there are various aetiology processes that present a role in the development of ME/CFS (Fernandez et al., 2009; Lorusso et al., 2009).

At present, there are 20 sets of diagnostic criteria for ME/CFS (Castro-Marrero et al., 2017). Currently, there is no “gold standard” diagnostic criteria, due to the lack of scientific evidence (Twisk, 2014; Clayton, 2015). In previous times ME/CFS was considered to be a side effect of other fatigue related medical conditions (Brurberg et al., 2014). Currently, to diagnose ME/CFS, it is a matter of excluding the existence of other underlying fatigue related conditions, even though ME/CFS is now classified as an independent medical condition (Brurberg et al., 2014). However, three criteria have been developed in more recent years that are deemed to be the most reliable and most utilised when diagnosing ME/CFS (Jason et al., 2004), with these

being: the Fukuda Criteria (1994), the International Consensus Criteria (2011) and the Canadian Consensus Criteria (2003) (Sunnquist et al., 2017). Although these surveys have their strengths and weaknesses, they are currently used as the predominant diagnostic criteria due to the broad analysis of symptoms and severity assessing the prime symptoms of the disease (Carruthers et al., 2011).

The Fukuda Criteria was developed in 1994 and has strict criteria that needs to be met for a ME/CFS diagnosis. It requires that "fatigue results in substantial reduction in previous levels of occupational, educational, social, or personal activities by greater than 50%" (Jason et al., 2016). To be diagnosed using the Fukuda (1994) Criteria, an individual must experience persistent or relapsing fatigue that lasts for longer than 6 months, as well as at least 4 of the following eight other symptoms: sore throat, lymph node pain, muscular pain, joint pain, post exertional malaise, new or different types of headaches, memory and/or concentration difficulties (cognitive deficiencies) and unrefreshing sleep (Jason et al., 2015). The Fukuda CFS criteria is considered to be the most commonly utilised criteria when diagnosing ME/CFS (Vink and Vink-Niese, 2018). Unfortunately, it has been identified that using just the Fukuda criteria for diagnosis is not considered adequate due to the variation of symptoms experienced by those with ME/CFS (Jason et al., 2015). The Fukuda Criteria does not explicitly require one to experience core symptoms of ME/CFS (PEM, cognitive dysfunction and unrefreshing sleep) and because some individuals do not experience these core symptoms, it has been suggested that greater diagnostic criteria are required to diagnose ME/CFS (Evans and Jason, 2018).

The Canadian Consensus Criteria (CCC) was developed in 2003, with this criteria defining ME/CFS as a fatigue related illness that persists for at least 6 months (Jason et al., 2016). Jason et al., *(*2016), suggests that to diagnose ME/CFS using the CCC, one must experience a marked degree of a new onset of unexplained, persistent or recurrent physical or mental fatigue that leads to a substantial reduction in all aspects of activity levels. There also needs to be unrefreshing sleep present, along with two or more neurocognitive manifestations such as confusion, inability to concentrate or memory loss/issues. Finally, there also needs to be at least one symptom from the three following categories: autonomic manifestations (light headedness, dizziness), neuroendocrine manifestations (flues, fevers, cold extremities) and/or immune manifestations (recurrent sore throats, painful lymph nodes). A significant aspect missing from this criteria that is now considered crucial when diagnosing ME/CFS (Holtzman et al., 2019), is PEM. The CCC criteria doesn't highlight PEM as being a core symptom of ME/CFS,

meaning individuals completing this criteria do not need to experience PEM to be diagnosed with ME/CFS, thus highlighting the importance of using more than one criteria for diagnosis.

Finally, the most recent criteria that is utilised is the International Consensus Criteria (ICC), which was presented in 2011. According to Carruthers et al., (2011), to meet the ME/CFS criteria utilising the ICC, one must experience PEM, at least one neurological impairment from the following 3 categories, neurocognitive impairments, pain, sleep disturbance or neurosensory, perceptual and motor disturbances. At least one of the following 3 immunity impairments, reoccurring flu like symptoms, overly susceptible to viral infections, sensitivities to food, odours or chemicals, and at least one energy metabolism impairment such as loss of thermostatic stability or intolerance of extreme temperatures (both hot and/or cold). Although this set of criteria does include PEM as being a crucial diagnostic symptom, there are other core symptoms missing, such as, unrefreshing sleep.

Even though more recently, greater means for the diagnosis of ME/CFS have been developed and are more readily available, work still needs to be completed to provide a criteria that incorporates all of the suggested core symptoms experienced by individuals, to take into account the variation of symptoms experienced by those thought to have ME/CFS. In saying this, it is now crucial to utilise all three of the criteria above to ensure all of the core symptoms are being covered in the diagnosis of ME/CFS (Jason et al., 2004).

2.4 Post Exertional Malaise (PEM)

For individuals with ME/CFS, the fatigue experienced following exercise is reported as post exertional malaise. PEM results in notable functional impairment beyond what is usual (Institute of Medicine, 2015), and is one of the most defining features of ME/CFS (Holtzman et al., 2019). PEM often leads to the exacerbation of symptoms, such as impaired cognitive function (Carruthers et al., 2003), sleep disturbance, symptoms associated with autonomic dysfunction including postural orthostatic intolerance, postural orthostatic tachycardia syndrome, light and sound sensitivity and/or gastrointestinal distress (Keller, Pryor and Giloteaux, 2014). PEM is defined as fatiguability that is present following a minor degree of physical exercise, potentially lasting three or more days following exercise but differs between individuals (Jason et al., 2015). It has been suggested that PEM symptoms can take up to 7 days to resolve following a single exercise session (Carruthers et al., 2003), hence why it is utilised as the predominant subjective marker when diagnosing ME/CFS (Twisk, 2014).

When examining PEM, it is often considered to have two focuses (McManimen, Sunnquist and Jason 2019), one being generalised full body fatigue and the other specific muscular fatigue. Generalised full body fatigue is often felt post exercise and is the feeling of greater fatigue than normal, everywhere on the body. Specific muscular fatigue is experienced when muscle groups such as the quadriceps are fatigued (sore and heavy) post exertion (McManimen, Sunnquist and Jason 2019). PEM has been proven to exacerbate other symptoms of ME/CFS along with increasing the loss of functional capacity (Holtzman et al., 2019). This is where it becomes crucial to prescribe appropriate durations, intensities and frequencies of physical activity to those with ME/CFS. It has been previously established that exercise can increase fatigue and PEM in those with ME/CFS (Loy, O'Connor and Dishman, 2016) and following a bout of moderate to vigorous exercise, PEM is often experienced and exacerbated, compared to following a bout of low intensity exercise in those with ME/CFS (Loy, O'Connor and Dishman, 2016; Holtzman et al., 2019). There appears to be considerable variation of symptoms experienced by those with ME/CFS, with the PEM onset and duration of recovery varying greatly between individuals (Holtzman et al., 2019). It has been suggested that PEM is the most debilitating symptom of ME/CFS, affecting approximately 95% of those with ME/CFS (Cook et al., 2017).

2.5 Relationship between Heart Rate Variability and ME/CFS

One's heart rate (HR) is the number of heart beats over a one minute period (Spodick et al., 1992). Heart rate variability (HRV) is the term used to reference the fluctuation of time intervals between adjacent heartbeats (Shaffer and Ginsberg, 2017), and is referred to commonly as the "beat-to-beat" alteration of the HR (Singh et al., 2018). It represents the ability of an individual's heart to respond to both physiological and environmental stimuli (Kim et al., 2018). HRV is defined by Hansen et al., (2012) as an underlying physiological mechanism relating to psychological functioning (cognition, emotional and self-regulation), fatigue, pain and stress of those with ME/CFS. It is a measure of the sympathetic and parasympathetic influences on the heart rate, thus providing information regarding the capacity for regulating emotional responses as well as assessing overall functioning of the cardiovascular system (Hansen et al., 2012; Singh et al., 2018). Essentially HRV is utilised as a mechanism to assess the productivity of the central nervous system and tracking natural fluctuations within the central autonomic network across various time spans (Escorihuela et al., 2020).

In previous research conducted, there has been a significant correlation made between HRV and those with ME/CFS. Hansen et al., (2012) discussed that those with ME/CFS characterised a higher resting heart rate compared to the healthy control subjects. It has been identified that there are differences within the HR parameters (resting HR, resting HR variability, HR response to and during head-up tilt, orthostatic HR, daily average HR and HR recovery), which indicates that those with ME/CFS may experience altered autonomic cardiac regulations compared to healthy controls (Nelson et al., 2019). Nelson et al., (2019), also suggests that these changes within HR parameters could be considered symptoms of the condition. Research conducted by Escorihuela et al., (2020), discovered that there is a positive relationship between HRV and ME/CFS, due to the apparent autonomic nervous system (ANS) dysfunction leading to the increase of sympathetic hyperactivity, which is demonstrated through the low frequency band (LF) variability, thus contributing to fatigue severity in those with ME/CFS. It has also been identified that a low HRV based upon the average of intervals between successive heartbeats (AVNN), standard deviation of intervals between successive heartbeats (SDNN), root mean square of successive differences in heartbeats (rMSSD) and proportion of normal-to-normal heartbeat intervals greater than 50ms (pNN50), have been associated with high scores (obtained through a self-reported questionnaire score) for fatigue, autonomic dysfunction, sleep quality, anxiety and depression in individuals with ME/CFS (Escorihuela et al., 2020). Having established the current relationships between HRV and ME/CFS, an area that does require further examination could be the effects that cardiopulmonary exercise testing (CPET), has on HRV in those with ME/CFS. This would provide further concrete details on the effects that exercise specifically has on HRV within this population.

2.6 Relationship between Cognitive Function and ME/CFS

Cognitive functioning is decreased in those with ME/CFS, compared to healthy counterparts (Nijhof et al., 2016). It has been established that deficits in cognitive performance are associated with physical fatigue and are often caused by a physiological fatigue related delay in neurotransmitter mechanisms (Thomas and Smith, 2009). Essentially meaning that due to the overall physical and mental fatigue experienced by those with ME/CFS, the speed at which neurotransmitters are signalling the body is heavily reduced, causing a delay in cognition (Thomas and Smith, 2009). Cognitive function is derived from cognition which incorporates internal mental processes that trigger how individuals perceive, remember, speak, think, solve problems and make decisions (Roy, 2013). Cognitive function is then utilised to describe varying components of the mind such as memory, attention span, reaction time and concentration (Benjafield, Smilek and Kingstone, 2010). Cognitive impairments can create

significant challenges in particular aspects of life due to the importance that cognition plays on the ability to learn, solve problems, remember and appropriately utilise information stored within the mind (Morley et al., 2015). It has been identified that lifestyle interventions such as cognitive training, moderately intensive physical exercise and diet may aid with the overall improvement of cognitive function in healthy populations (Kasper et al., 2020). However, this may not necessarily be beneficial for those with ME/CFS, due to the ongoing fatigue that undergoing these potential interventions will continue to cause. This is where ME/CFS research becomes crucial when prescribing interventions to improve symptoms experienced by individuals.

It has been identified that approximately 85-95% of those diagnosed with ME/CFS will also experience cognitive impairments such as slow thinking, difficulty focusing (particularly for extended periods of time), confusion, inability to concentrate, forgetfulness and/or haziness/fogginess ('brain fog') in thought processes (Chaudhury, 2014). In a study conducted by Robinson et al., (2019), it was highlighted that there is a significantly positive relationship between ME/CFS and reduced cognitive performance. A particularly notable discovery was the reduction in basic processing speed (through the digit span, and Stroop tests), that may have potential flow-on effects on other cognitive domains (Robinson et al., 2019). Evidence suggests that the existence of impairments surrounding focused attention, speed of processing and performance accuracy in those with ME/CFS is apparent and, can be supported by data that indicates that even when healthy individuals become significantly sleep deprived, they become more fatigued and cognitive deficits become more pronounced (Morley et al., 2015). Thus, identifying fatigue, whether it be physical or mental, can cause a depletion in cognitive functioning regardless of whether the individual is considered to be healthy or diagnosed with ME/CFS. Due to the consistent fatigue experienced by those individuals with ME/CFS, it can be highlighted that cognitive difficulties are experienced on greater numbers of occasions compared to that of healthy individuals (Morley et al., 2015).

2.7 Relationship between Exercise and ME/CFS

Scholarly research has suggested notable disparity regarding the relationship between exercise and ME/CFS, with some research suggesting physical exercise exacerbates ME/CFS symptoms for a period of time following exertion (considered PEM) (Loy, O'Connor and Dishman, 2016), and others demonstrating that it can provide long term benefits such as improved strength and endurance (Fulcher and White, 1998). With this in mind, it may be that some individuals may benefit from exercise and may experience a positive effect on fatigue levels over time, sleep, cognitive functioning, physical function and general self-perceived health (Larun et al., 2017; Wilshire et al., 2018), but currently it is not possible to categorise individuals into either group. Exercise has demonstrated positive effects on individuals with ME/CFS, with physical deconditioning being reduced (Dannaway et al., 2017). Davenport et al., (2010), recommends that aiming for a 10% margin below the estimated target heart rate, which has been suggested to be 55% of one's age predicted max heart rate (APMHR) (Van Campen, Rowe and Visser, 2020), will provide a critical threshold for self-management of ME/CFS. This is supported by other studies, where aiming for lower intensities between 45-55% of APHMR (Davenport et al., 2010; Van Campen, Rowe and Visser, 2020), more frequently is recommended (Larun et al., 2017; Wallman et al., 2005). Repeated exercise has demonstrated that individuals with ME/CFS have a significantly decreased exercise capacity compared to control patients/general populations (De Becker, 2000), which may not be just as a result of deconditioning. However, consistent, light aerobic exercise aiming for a HR of between 45-55% of APMHR (Davenport et al., 2010; Van Campen, Rowe and Visser, 2020), has been found to have minor long term benefits on the cognitive deficits experienced by those with ME/CFS such as speed, consistency and efficiency of cognitive functioning (Cook et al., 2005). One-off bouts of light exercise (45-55% APMHR, Davenport et al., 2010; Van Campen, Rowe and Visser, 2020), showed no sign of any improvements nor exacerbations in cognitive functioning of those with ME/CFS, potentially showing that repetitive, light bouts of aerobic activity is more beneficial for cognitive functioning in those with ME/CFS (Cook et al., 2005). This lack of change may suggest that there is a refractory period where symptoms are not exacerbated, but further research in this area to provide greater intelligence and evidence is required. It has also been discovered that moderate to vigorous aerobic activity (HR >55%) for extended durations of time (>40minutes), significantly increases general levels of fatigue and PEM in ME/CFS patients, compared to the much smaller impact light activity has on fatigue and PEM (Loy, O'Connor and Dishman, 2016). Light exercise may increase levels of PEM and fatigue immediately following exercise, but long-term it has been seen to greatly reduce these

symptoms, however this research used the Fukuda 1994 criteria (De Becker, 2000) where patients do not need to have PEM.

Fulcher and White (2000), conducted research surrounding the effect of exercise on fatigue in those with ME/CFS, finding that acute exercise (a single treadmill step walking test for a mean of 10 minutes, beginning at 5kph, with an increase of 2.5% every 2 minutes), increases overall fatigue levels (including muscular fatigue), immediately following exercise bouts, with severity being dependent on intensity, duration and type of exercise. However, fatigue levels initially following a bout of exercise progressively decreased over time (Fulcher and White 2000). Individuals that are affected by ME/CFS, tend to have significantly lower exercise capacities, generic low physical fitness, and high body mass ratio due to sedentary lifestyles compared to their comparative sedentary control subjects (Loy, O'Connor and Dishman, 2016). To counteract and manage these fatigue levels along with managing PEM, strategies such as 'pacing' have been developed and recommended, to encourage patients to balance activities with rest (Van Campen, Rowe and Visser, 2020). There is much criticism stemmed towards exercise prescription that was thought to be beneficial such as Graded Exercise Therapy (GET). There are many short comings that have come to light in earlier years, suggesting that training that involves frequent activities above Anaerobic Threshold (AT), exacerbates deterioration in physical functioning (Van Campen, Rowe and Visser, 2020).

Due to much of the current criticism and short comings of exercise beyond AT that has come to light in recent years, repeated exercise to submaximal levels is widely becoming a protocol utilised within clinical populations that are characterised by fatigue and PEM (Lindheimer et al., 2020). Several studies into repeated exercise on fatigue and PEM have been completed in recent years (Hodges et al., 2020; Hodges, Nielsen and Baken, 2018; Bouquet et al., 2019; Van Campen, Rowe and Visser, 2020), with the aim of assessing the effects of exercising to AT on ME/CFS and more specifically PEM. Repeated exercise testing is widely used for ME/CFS studies to assess functional impairment, by first of all providing a measure of baseline functional ability, with the repeated test aimed to provoke PEM, for an assessment of the effects of PEM on the predetermined baseline functional capacity (Stevens et al., 2018). In order for repeated exercise challenges to be useful in this setting, it is important to carry out breath-by-breath gas analysis. This gas exchange (oxygen and carbon dioxide ratio) (Lim et al., 2020), provides a greater understanding of functional capacity, along with illness severity and characterisation, with emphasis being placed on measuring $\dot{V}O_2$peak, due to this being a major objective marker of functional capacity in the ME/CFS population (Stevens et al., 2018). Along

with analysing functional capacities, conducting repeated exercise with ME/CFS patients, provides an assessment platform for recovery capacity, with special attention paid to energy production and the effects of PEM on recovery (Lim et al., 2020). In addition, repeated 2-day CEPT is becoming an increasingly popular method to differentiate fatigue differences between ME/CFS patients and control subjects (Nelson et al., 2019). This factor has come about since the discovery that those with ME/CFS are more frequently reaching onset of AT earlier compared to healthy counterparts (Nelson et al., 2019). However, in saying this, it has also been suggested that more evidence is required to confirm the effectiveness of repeated exercise, with the diagnosis of ME/CFS. Repeated exercise testing is becoming more prominent when it comes to testing within studies assessing ME/CFS. It is providing an opportunity for evidence based data on aspects of ME/CFS that have previously been unable to be assessed which is encouraging for researchers in this area.

2.8 Treatment

Recent research suggests that there are no pharmalogical treatments/cures, such as approved-drugs for ME/CFS, however, there are various medications and/or methods that can be used in order to relieve and/or manage the symptoms experienced such as pain killers for pain, and antibiotics for infections (Castro-Marrero et al., 2017). Lifestyle changes can also be appropriate for the management of ME/CFS related symptoms, to reduce fatigue levels, such as a reduction in physical activity or activities that require strenuous amounts of concentration for extended periods of time (Roberts, 2018). The most researched treatment method for ME/CFS is considered to be light exercise, with Fernandez et al., (2009), suggesting that along with cognitive behaviour therapy, gradual, light exercise has demonstrated significant efficacy in patients that have been diagnosed with ME/CFS. To date, studies have indicated that low intensity exercise prescription may be beneficial to the ME/CFS population (Larun et al., 2017; Wallman et al., 2005; Loy, O'Connor and Dishman, 2016), however, not much has been investigated in the way of frequency, duration, or type of exercise. As previously mentioned above, gradual graded exercise has been deemed to be a physical treatment method that could be prescribed to those with ME/CFS, however a number of shortcomings have been found within these available studies. Current research conducted by Robinson et al., (2019), advocates that considering the prevalence of ME/CFS, there is no current curative treatment that can be prescribed.

Cognitive behaviour therapy has demonstrated that it may be a beneficial treatment for areas such as concentration and memory for those with ME/CFS (Fernandez et al., 2009).

Participating in cognitive behaviour therapy has been seen to improve symptoms of ME/CFS and functional ability as well as aiding individuals return to the work force gradually (Butler et al., 1991). Cognitive behavioural therapy can be effective with treating symptoms of fatigue, mood and physical fitness (O'Dowd et al., 2006), however, current studies lack understanding around the beneficial effects it may have on cognitive and physical functioning for those with ME/CFS. Cognitive behaviour therapy provides emphasis on how a person feels and acts and thus can help individuals recognize how their own personal fears of participating in activity (any form of), can lead to, or predetermine certain behaviours, which ultimately instigates feelings of greater fatigue (Yancey and Thomas, 2012). Cognitive behavioural therapy can have positive impacts by reducing the levels of fatigue, depression and anxiety in individuals, along with having positive effects on work and social adjustment and post-exertional malaise (Yancey and Thomas, 2012). Many researchers support the prescription of cognitive behaviour therapy for those with ME/CFS, however, this is not without scrutiny from others (Vink and Vink-Niese, 2019; Yancey and Thomas, 2012), with greater and more recent studies being required in this area to assess the current views on cognitive behaviour therapy as a form of treatment for ME/CFS.

2.9 Summary

As established, ME/CFS is a chronic condition with many grey areas surrounding differing aspects of the condition. Although research is providing more detailed information on diagnostic and treatment areas of ME/CFS, further studies are essential to understand the full picture and remove much of the contradicting information that has been established. Although there are many theories regarding the aetiology of ME/CFS, this remains an aspect of ME/CFS that is still widely unknown. Many theories currently suggest that there is not necessarily one contributing factor to the cause/development of ME/CFS, and instead it is a combination of factors surrounding the central nervous system. Although diagnostic measures are becoming more understood, a lot of controversy remains around the diagnosis of ME/CFS. Currently there are 3 diagnostic criteria that are predominantly utilised with those being the Fukuda Criteria, the International Consensus Criteria and the Canadian Consensus Criteria. These criteria provide a basis for symptom recognition, however, a more universal and thorough criteria needs to be established to ensure diagnosis of ME/CFS becomes easier in the future. PEM has been identified as the most predominant subjective marker for ME/CFS and provides the basis for many current and past studies into ME/CFS. It has widely been researched and recently been used to provide greater information particularly surrounding the relationship of exercise and ME/CFS. In saying this, there are still many question marks surrounding exercise

prescription to those with ME/CFS, and although current research is providing greater details, the complexity of ME/CFS and the variation of symptoms and symptom severity among individuals is providing challenges within this area. To date, there are no curative treatment options for ME/CFS and instead, management of symptoms through the use of exercise prescription and other medicinal methods such as painkillers and antibiotics to treat the symptoms experienced by those with ME/CFS are being recommended. Overall, research into aspects of ME/CFS remains very immature however, there are many studies that are being conducted that are providing interesting information that will aid with understanding of this condition to greater extents, particularly regarding exercise prescription as a management or treatment of ME/CFS.

CHAPTER THREE: AIMS AND HYPOTHESES

3.1 Introduction

From analysis of the extended amounts of literature and previous research studying ME/CFS, it has been clearly identified that treatment and management plans for those with ME/CFS is a part of this broad topic that requires a lot more research. Many research studies have identified the effects of exercise on those with ME/CFS along with diagnostic criteria, yet none have identified safe exercise guidelines to ultimately reduce fatigue and fatigue related symptoms. The purpose of this study was to investigate the physiological and cognitive effects of a five minute exercise challenge at AT on those with ME/CFS, whilst aiming to identify safe exercise guidelines, for the treatment and management of fatigue and fatigue related symptoms, particularly PEM and physiological variables (such as, blood pressure, heart rate, $\dot{V}O_2$, and respiratory exchange ratio) that are often exacerbated post exercise.

3.2 Aims

The main aims of this evidence-based research through applying a series of biomedical tests were:

1. Examine the effects of a 5-minute repeated exercise challenge at anaerobic threshold on:
    a) Physiological variables: Heart Rate, Blood Pressure, $\dot{V}O_2$, Rating of Perceived Exertion, Respiratory Exchange Ratio.
    b) Post Exertional Malaise.
    c) Heart Rate Variability.
    d) Cognitive Functioning.
2. Develop exercise guidelines to aid with the treatment and management of ME/CFS.

3.3 Hypotheses

Following the maximal exercise test, individuals will experience great amounts of fatigue and PEM, but type and severity of symptoms will greatly vary between individuals. It is also hypothesised that following the repeated exercise challenge at a lower intensity and duration than the maximal test, individuals will experience less fatigue and fatigue related symptoms, providing more information surrounding the physiological response to exercise experienced by those with ME/CFS.

CHAPTER FOUR: MATERIALS AND METHODS

4.1 Overview

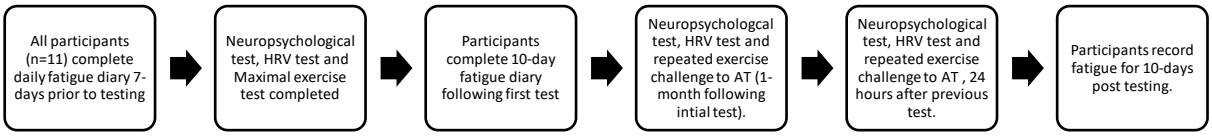

Figure 1 Basic overview of testing procedures and protocol.

4.2 Participant Recruitment

Participant recruitment was primarily completed through local ME/CFS Associations in the Manawatu and Wellington regions along with National ME/CFS Society Groups within New Zealand. This was initially executed by Dr. Lynette Hodges through the use of presentations and followed by word-of-mouth between those in these associations. Interested participants completed the De Paul symptom and SF-36 screening questionnaire. These were then analysed to ensure participants met the International Consensus Criteria, the Canadian Criteria (Carruthers et al., 2003) and the Fukuda et al., (1994) ME/CFS Case Definition Criteria. Participants that met the criteria were contacted via email and invited to participate in the study. Once confirmation of involvement had been received by the potential participants, they were sent a detailed information sheet that contained information regarding protocols, expectations and rights (see appendix 9.1). They were also sent a 7 day fatigue diary, which they were asked to complete the 7 days prior to commencing any testing (see appendix 9.2). Participants were also asked to complete a health and medical questionnaire along with informed consent (appendix 9.1) prior to exercise testing. The study was approved by the Health and Disabilities Ethics Committee (18/CEN/183).

The sample size of this study was calculated by analysing previous research conducted by Hodges et al., (2020), where physiological responses were identified at an Anaerobic Threshold $\dot{V}O2$ range of 13.5-15.0 $ml{\cdot}kg{\cdot}min^{-}1$, with a standard deviation of 2.6-3.8, a power of 54.4-63.8W and a significance level of 0.05. For this testing, a cohort of 11 participants was considered adequate, however, having a cohort of 20 participants would have made for a stronger basis of research.

4.3 Procedures and Protocols

A cohort of 11 participants were recruited. Once the above recruitment was completed, participants were briefed on procedures and protocols. Following a 5 minute seated period, baseline measurements were taken, such as resting blood pressure using a sphygmomanometer and a stethoscope, height using a stadiometer (Seca, Bonn, Germany; accurate to 0.1com) and body weight using electronic scales (Hiweigh technologies Ltd, Shanghai, China: model X3, accurate to 0.02kg), were measured prior to exercise testing. Upon each visit, HRV was recorded using the HRV4Training app which required participants to lie down for 5 minutes then stand for 5 minutes. Participants then completed a series of neuropsychological tests on a computer which included tests such as the Stroop, trial, word recall, reverse digit span and choice tests to assess their pre-exercise cognitive functioning.

Upon the first visit, participants completed a maximal cardiopulmonary exercise (CPET) test through an incremental cycle ergometer exercise test, as described by Hodges, Nielsen and Baken, 2018. The cycle-ergometer (Excalibur Sport, Lode, Netherlands) was set up to the correct height for each participant, with approximately a 5-degree bend at the knee during extension. Participants aimed to maintain 60-80 revolutions per minute (rpm) throughout the challenge and were encouraged to participate until they reached voluntary exhaustion or until a $\dot{V}$O2peak was reached identified by a plateau in $\dot{V}$O2 despite an increase in work rate (Edvardsen, Hem and Anderssen, 2014). The test was terminated when the ACSM (2014), termination criteria were met, such as a drop in systolic blood pressure (SBP) by >10mmHg, an excessive rise in blood pressure (>250/115mmHg), abnormal HR response, angina like symptoms and/or signs of poor perfusion or if the participant requested to stop. The workload increased at a rate of 5watts/20seconds (15watts/minute) and was recorded each minute. Breath by breath, oxygen uptake ($\dot{V}$O2), carbon dioxide production (VCO2), and respiratory exchange ratio (RER) were collected through 10 second intervals using the online gas analysis software, Turbofit (Version 15, VacuMed, Ventura, CA, USA).

Participants then remained seated on the cycle ergometer and were further monitored for 2-5 minutes during recovery. HR using HR monitors (Polar FT1, Polar Electro, Finland) fitted to participants and rating of perceived exertion (RPE) (Borg 6-20 scale) (Borg, 1982), were measured and recorded each minute of the challenge along with blood pressure, using a sphygmomanometer every 2 minutes. Following this, participants were given and asked to

complete a 10-day fatigue diary. This was to monitor fatigue related symptoms and determine when they believed they had returned to their "normal" level of fatigue.

Oxygen consumption rate, workload and HR at AT were obtained using the V-Slope method (Wasserman, Beaver and Whipp, 1990). This information was used to retrieve data for target HR and workload by referring to the HR and workload recorded during the $\dot{V}O2$ peak test.

The second and third visits consisted of the same tests prior to exercising, such as resting BP and HR, height and weight, neuropsychological tests and HRV tests, however, participants completed a cycle ergometer exercise challenge at a pre-calculated resistance (calculated (calculated using the V-slope method from the maximal CPET test), for 5 minutes with breath-by-breath gas samples through online gas analysis using Turbofit software being measured along with HR, and RPE every minute, and BP every three minutes. They then completed a cool-down at 15 Watts resistance for approximately 5 minutes or until their heart rate dropped to around resting. Participants then returned to the laboratory 24 hours later to complete the same series of tests, to assess the impact of the exercise challenges on cognitive functioning, HRV and physiological factors such as $\dot{V}O2$, respiratory exchange ratio (RER), RPE, HR, SBP, and diastolic blood pressure (DBP). Following the third and final exercise challenge, participants were asked to complete a 10-day fatigue diary to record the symptoms experienced during their recovery and their personal length of recovery (how many days it took for them to return to their 'normal'). Participants were also asked to answer a set of exercise recovery questions (refer to appendix 9.3), for us to gain an understanding of how the participants felt following the series of exercise tests.

4.4 Statistical Analysis

The Statistical Package for Social Sciences (SPSS version 25.0, IBM, New York, USA), was utilised when analysing all of the data. The analysed data is presented in the tables in the results section of this text. The statistical significance was programmed at <0.05 and all of the results were presented as mean (standard deviation).

Data for all groups were examined for normality using the Sharprio and Wilk test for normality. The data were analysed using a paired sample t-test (2-tailed) to identify differences between the repeated exercise challenges completed by the participants. Subjective measures of fatigue were recorded pre ($\dot{V}O2$Peak test) and post-test ($\dot{V}O2$Peak test and 2x AT tests) (using a scale of 1-10) and total time for recovery (days) using the fatigue diaries (appendix 9.2).

CHAPTER FIVE: RESULTS

5.1 Participant Characteristics

From the sample of 11 individuals, 9 (81.82%) of them were female, with just 2 (18.18%) of them being males. However, this higher ratio of female participants aligns with the distribution considered "normal" for ME/CFS. Cortes-Rivera *et al* (2019), established that ME/CFS has a 3:1 ratio, females to males respectively. Of the 11 participants, 10 were over the age of 40 years old, with one individual being 28 years old. This distribution aligns with normative data suggesting ME/CFS is most prevalent in people aged between 20-50 years of age (Shafran, 1991), with peak onset occurring in two age peaks with these being 10-19 years of age and 30-39 years of age. (Collin et al., 2015). Table One provides the means and standard deviations (SD) of participant characteristics including body mass index (BMI) which is considered to be on the higher end of the scale for this population. A healthy or 'normal weight' BMI is considered to be between 20 and 24.9, with an overweight classification being 25-29.9 (Nuttall, 2015). Thus information then suggests that based on the mean, the participants have a BMI considered overweight.

Table 1: Participant Descriptive Characteristics.

	Mean	**SD**
Age (years)	49	14
Height (cm)	168	9
Weight (kg)	80.3	18.4
BMI (kg/m^2)	28.79	7.58

Key: BMI = Body Mass Index.

5.2 Physiological Results.

Table Two displays physiological results from the cardiopulmonary exercise tests completed on all participants. The mean $\dot{V}O_2$ peak of 23.36 ml·kg·min^{-1} is considered low compared to the predicted $\dot{V}O_2$peak for age/sex matched sedentary 'healthy' populations (American College of Sports Medicine, 2013). RER follows a normal response to exercise with all achieving levels required for a maximal exercise test. RPE is within the expected range (>18 on Borg 6-20 scale)(Fletcher et al., 2001), given the intensity of the activity. Both systolic and diastolic blood pressure are considered high relative to the mean HR and workload, but are as to be expected for a maximal incremental exercise test. PeakHR is considered to be relatively low based on normative data (Panton et al., 1996), which suggests the range for APMHR (peakHR) is 171

bpm, for 18-65 year old's respectively. However, in relation to the low $\dot{V}O2$ Peak achieved by participants the peakHR is relative. From the 11 participants in this study, just one individual reached their APMHR during the max CPET. When comparing the mean PeakHR and the mean APMHR it is clear to see that the AMPHR is considerably higher than the actual peakHR reached by participants. Nine of the 11 individuals did reach 85% (+/- 5%) of their APMHR, with only two individuals reaching 77% of their APMHR. Mean $\dot{V}O2$ Peak is considerably low relative to the HR, BP, RER, RPE and W response.

Table 2: Max CPET Physiological Data.

	Mean (SD)	**SD**
$\dot{V}O2$ Peak (ml·kg·min^{-1})	23.36	7.59
RER Peak	1.07	0.091
HR Peak (bpm)	155	13.58
RPE Peak (6/20)	18	1.54
SBP Peak (mmHg)	169	26.49
DBP Peak (mmHg)	97	12.72
Power Output Peak. (W)	131	60.41
APMHR	171	13.81

Key: $\dot{V}O_2$ = Oxygen Consumption; RER = Respiratory exchange ratio; HR = Heart Rate; RPE = Rating of Perceived Exertion; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; APMHR = Age Predicted Max Heart rate.

Table Three depicts the $\dot{V}O_2$, power output and HR at Anaerobic threshold as calculated using the data from the max CPET and the V-Slope method. The mean $\dot{V}O_2$ of 15.69 ml·kg·min^{-1} at AT is considered considerably low, as well as the mean power output of 68W. However, all 3 values are relative to each other with a low $\dot{V}O_2$ expected with a power output of 68W and a HR of 125bpm, although these figures are considered low.

Table 3: Physiological data at Anaerobic Threshold defined by V-Slope Method.

	Mean	SD
$\dot{V}O2$ (ml·kg·min^{-1})	15.69	5.26
Power (W)	68	29.52
HR (bpm)	125	18.38

Key: $\dot{V}O_2$ = Oxygen Consumption; HR = Heart rate.

Table Four illustrates the physiological data from the repeated 5 minute exercise challenge, 24-hours apart, at least a month following the max CPET. $\dot{V}O2$ was the only factor recorded where there was a significant difference (P-value = 0.006) between the first exercise challenge at AT and the repeated challenge. There was a drop in $\dot{V}O2$ between the two exercise challenges, which demonstrates that aerobic capacity declined between the two tests, potentially due to the inability of this population to recover from exertion within the time frame between the two tests. Both mean SBP and mean DBP are considerably high relative to HR and workload across both days with both being greater during the repeated exercise challenge. By analysing $\dot{V}O_2$, RER and RPE, it is evident that individuals are exercising to AT, however 6 of the 11 participants have an HR and BP response equivalent to exercising >84% of their peak recorded data from the initial max CPET. From the 11 participants, 4 individuals increased their heart rate beyond the 70% threshold based on their target percentage of APMHR. With the other 7 individuals increasing their HR to around 125bpm which falls within the AT threshold.

Table 4: Physiological Data from Repeated Exercise Challenge to AT.

	Test 2 - Mean(SD)	Test 3 - Mean (SD)	P-Value
$\dot{V}O2$ (ml.kg.min)	18.7 (6.77)	16.01 (5.87)	0.006
RER	0.91 (0.11)	0.91 (0.93)	0.562
HR (bpm)	124 (28)	117 (24)	0.159
RPE (6/20)	14 (2.3)	13 (2.82)	0.542
SBP (mmHg)	169 (33.11)	177 (34.53)	0.138
DBP (mmHg)	96 (17.76)	100 (23.27)	0.32
Power Output (W)	68 (29.52)	68 (29.52)	

Key: $\dot{V}O_2$ = oxygen consumption; RER = respiratory exchange ratio; HR = Heart rate; RPE = rating of perceived exertion; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Below are a series of graphs that illustrate the difference in mean HR, RPE, RER, BP and workload between the first 5 minute exercise challenge at AT and the repeated exercise challenge conducted 24-hours later. The graphs demonstrate the distribution of the means between groups one and two. With group one being the 7 individuals who increased their HR within the suggested AT threshold range. Group 2 represents the other 4 individuals who increased their HR beyond the 70% AT threshold based on their target percentage of APMHR. From these graphs we are able to see an illustration of how group one are exerting at a lower workload, yet they have a greater HR, RPE, RER and BP response to the exercise challenges. This further highlights the physiological response to exercise experienced by this population.

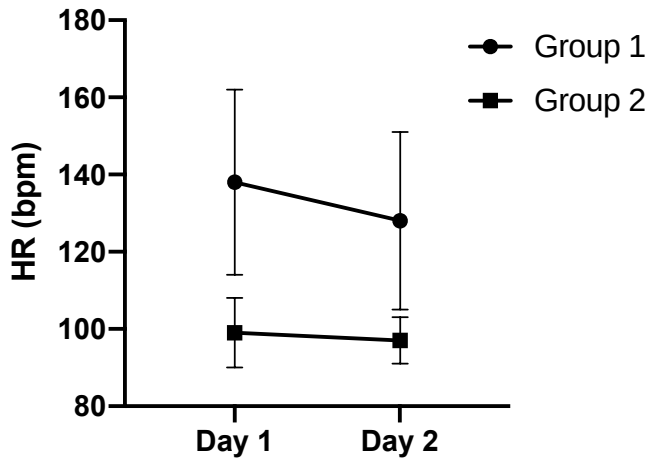

Figure 2: Heart Rate Comparison of a repeated exercise challenge.

Figure 2 Illustrates the heart rate of both Groups 1 and 2 (as highlighted above) across the repeated exercise challenge completed 24-hours apart. This graph demonstrates that group one has a much greater HR response to the exercise challenges compared to group two, despite that group one is exercising at a lower workload. Group one also has a more noticeable decline between days 1 and 2.

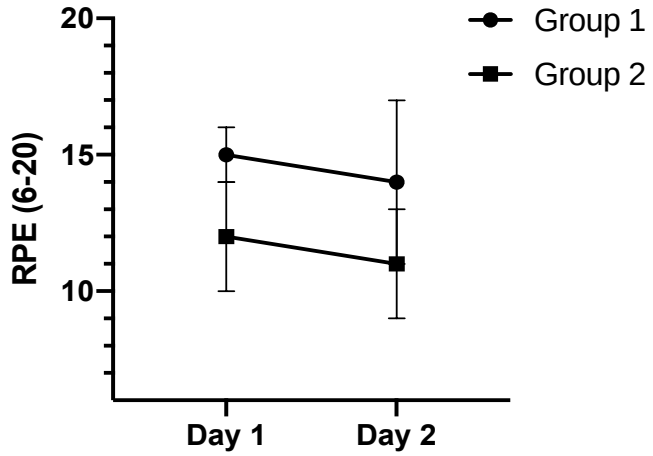

Figure 3: RPE Comparison of a repeated exercise challenge.

Figure 3 Compares the recorded RPE of groups one and two, between Day 1 and 2 of the repeated exercise challenges at AT. This figure shows that group one has a higher RPE than that of group two across both days, with a similar decline seen for both groups between days 1 and 2.

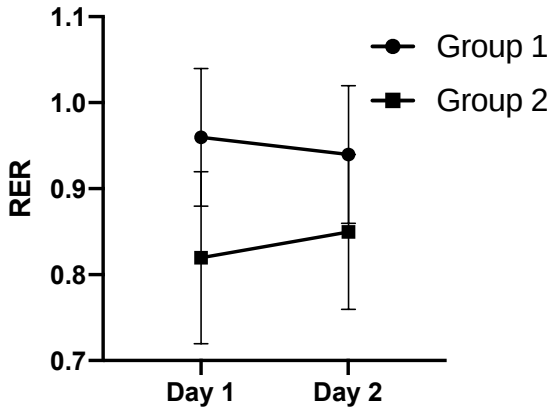

Figure 4: RER Comparison of a repeated exercise challenge.

Figure 4 Illustrates RER on Day 1 and Day 2 of the repeated exercise challenge at AT, with Groups 1 and 2 being compared. Figure 4 highlights that again group one have a higher RER response to the. Exercise challenges compared to group 2. One noticeable difference between these two groups is that the RER response of group one declines from day 1 to day 2, with group 2 having an in increase in mean RER between day 1 and day 2.

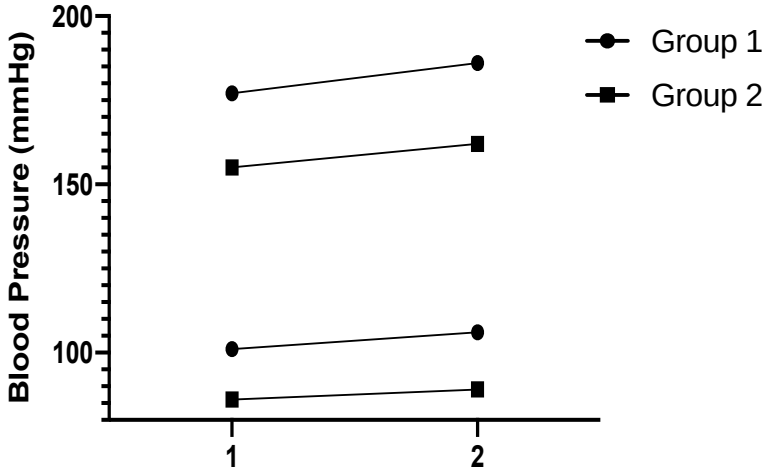

Figure 5: Blood Pressure Comparison of a repeated exercise challenge.

Figure 5 Provides a comparison of both SBP (top two lines) and DBP (bottom two lines), between Groups 1 and 2 derived from the data of the repeated exercise challenges at AT. For both SBP and DBP group one has a higher BP response to the exercise challenges for both day one and day two, with similar increase patterns being observed between groups.

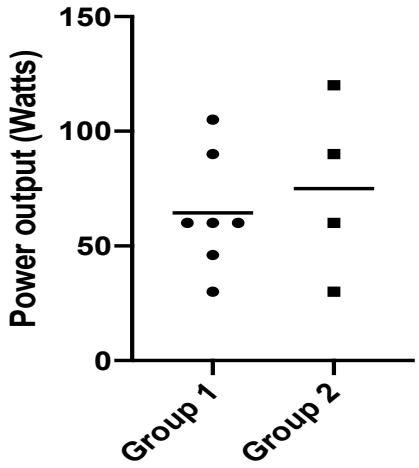

Figure 6: Power Output Comparison between Groups 1 and 2.

Figure 6 Compares the power output for the repeated exercise challenge of all 11 participants, grouped into the two groups. This illustrates that group one had a lower distribution of power output compared to group 2. This is an interesting observation due to group one having a greater physiological response regarding HR, RPE, RER and BP across both tests, suggesting that even though group one had a lower workload, their bodies are being put under greater amounts of physiological stress.

Table Five exhibits the mean HRV data from all three exercise challenges, along with the P-value between tests 2 and 3, to identify whether there are any significant differences. There are no significant changes to HRV, as identified by the high P-value figures.

Table 5: HRV data from all Exercise Challenges.

	Test 1 – Mean(SD)	Test 2 – Mean(SD)	Test 3 – Mean(SD)	P-Value
HR Lying	71.27 (10.64)	72.66 (14.36)	73.1 (12.5)	0.72
HR Standing	78.17 (15.46)	76.97 (16.24)	77.95 (19.5)	0.812
AVNN Lying	872.83 (142.53)	869.07 (182.21)	852.09 (149.52)	0.267
AVNN Standing	803.59 (170.1)	811.29 (178.31)	773.97 (270.81)	0.525
SDNN Lying	60.35 (41.41)	67.18 (77.06)	65.07 (63.52)	0.714
SDNN Standing	99.02 (105.97)	99.88 (94.37)	97.63 (101.73)	0.915
rMSSD Lying	42.79 (26.1)	56.24 (64.51)	56.4 (48.55)	0.987
rMSSD Standing	72.26 (100.07)	91.93 (105.2)	93.61 (112.3)	0.943
pNN50 Lying	14.82 (14.35)	20.25 (22.04)	23.89 (22.38)	0.535
pNN50 Standing	21.25 (20.72)	29.64 (26.92)	28.34 (27.4)	0.836
LF Lying	0.19 (0.16)	0.24 (0.32)	0.24 (0.31)	0.721
LF Standing	0.25 (0.29)	0.28 (0.32)	0.25 (0.29)	0.538
HF Lying	0.26 (0.23)	0.25 (0.32)	0.28 (0.36)	0.388
HF Standing	0.37 (0.34)	0.38 (0.46)	0.26 (0.32)	0.201

Key: HR = heart rate; AVNN = average of intervals between heartbeats (NN); SDNN = standard deviation of intervals between heartbeats; rMSSD = root mean square of successive differences between intervals of heart beats; pNN50 = proportion of normal-to-normal intervals of heart beats greater than 50ms; LF = low-frequency band; HF. = high-frequency band.

Table Six demonstrates the mean cognitive (neuropsychological) test data across all three tests, along with the P-value between challenges 2 and 3 to identify any significant differences between tests. For the majority of this data, there are not considered to be any significant differences across the three challenges, besides minor relevant improvements. The significant improvements can be seen in the recall number 1 and 2 tests, along with the completion time which improves significantly over the three exercise challenges as suggested by the P-values (0.001 improvement, 0.003 improvement and 0.015 improvement respectively). Thus, suggesting the repeated exercise challenge did not provoke detrimental effects on cognitive functioning. This improvement is considered normal, due to the nature of the testing, Participants complete the same series of neuropsychological tests, thus meaning individuals learn/remember aspects of the tests, causing overall improvements.

Table 6: Cognitive (Neuropsychological) Test Data from all Exercise Challenges.

	Mean (SD)	Test 2 – Mean (SD)	Test 3 – Mean (SD)	P-Value
StroopValid	48 (24.36)	56.64 (14.29)	54.18 (17.2)	0.628
StroopMean	0.61 (0.22)	0.63 (0.05)	0.6 (0.07)	0.157
StroopSD	0.125 (0.04)	0.13 (0.02)	0.13 (0.03)	0.53
TrialTime	89.76 (71.45)	71.96 (23.96)	68.38 (21.13)	0.403
RTValid	57.73 (1.85)	58.27 (1.35)	58 (2.49)	0.747
RTMean	0.55 (0.06)	1.33 (2.73)	0.52 (0.06)	0.344
RTSD	0.09 (0.016)	0.08 (0.02)	0.08 (0.017)	0.568
Digitspan	5.18 (1.89)	6.09 (1.64)	6.45 (1.63)	0.42
RecallNumber1	5.55 (2.07)	8.18 (2.79)	10.82 (3.49)	0.001
RecallNumber2	9.27 (3.04)	9.72 (2.45)	11.45 (2.11)	0.003
RecallNumber3	9.91 (2.81)	11.36 (2.62)	12.36 (2.66)	0.128
RecallNumberP2	8.18 (2.93)	10.36 (2.87)	11.91 (2.34)	0.075
RecallTime1	62.93 (38.64)	56.72 (22.66)	60.17 (31.8)	0.64
RecallTime2	63.61 (55.7)	63.38 (43.75)	55.03 (26.5)	0.341
RecallTime3	73.93 (72.43)	55.97 (20.66)	65.48 (39.11)	0.274
RecallTimeP2	93.16 (93.2)	75.15 (44.12)	76.95 (52.58)	0.779
Completion Time	1013.89 (198.73)	815.56 (145.14)	721.99 (96.59)	0.015

Key: RT = reaction time; RTSD = reaction time, standard deviation.

Table Seven outlines the mean number of days taken to feel as though the participants had recovered back to their 'normal'. From the repeated exercise challenge, it was determined that individuals did indeed take less time to recover (compared to recovery days from the $\dot{V}O2$ peak test), with fatigue related symptoms experienced not as debilitating compared to exercising to peak. This table also includes the P-value between the two types of challenges. From the P-value it can be determined that there is a significant difference between the recovery days (0.03) following the max CPET, compared to following the repeated exercise challenge at AT.

Table 7: Recovery Days Post Exercise Challenges.

	Post $\dot{V}O2$ challenge – Mean (SD)	Post AT challenge – Mean (SD)	P-Value
Recovery Day(s)	9.18 (2.64)	5.23 (4.01)	0.03

CHAPTER SIX: DISCUSSION

6.1 Overview

The purpose of this study was to investigate and report on the physiological and cognitive effects of a repeated 5 minute exercise challenge on those with ME/CFS, with the intention of being able to provide evidence based recommendations and guidelines of exercise, for the safe and beneficial treatment/management of symptoms of ME/CFS. The study examined $\dot{V}O2$ (ml.kg.min $^{-1}$), RER, HR (bpm), RPE (Borg 6-20), BP (mmHg) and Workload (W), during both maximal and submaximal exercise capacities. The physiological measures were compared within the group and between testing days. Secondarily, this study also investigated the effects of exercise on HRV and cognitive functioning, to assess whether participating in regular exercise enhanced or normalised HRV and cognitive function.

6.2 Statement of Findings

The results of this study identify information that both support and counter the original hypotheses, particularly the area surrounding the physiological response to submaximal exercise experienced by those with ME/CFS, thus providing more in depth information that can be utilised when prescribing exercise for treatment of ME/CFS. The initial hypothesis suggested that following the maximal CPET, individuals would experience great levels of fatigue and PEM symptoms, with the severity not being as great following the repeated exercise challenges. By large, this was the response seen from the participants. It was highlighted that due to the complexity and variation between individuals with ME/CFS, extent of fatigue and PEM symptoms varied greatly, with the common symptoms being muscular fatigue, brain fog, and general ongoing tiredness/fatigue. Physiological findings showed that those with ME/CFS have a reduced $\dot{V}O2$ peak compared to healthy control subjects from other similar studies. This can be supported by a meta-analysis study conducted by Franklin et al., (2019), where the primary finding was that patients with ME/CFS appeared to have a substantially reduced $\dot{V}O2$ peak compared to healthy controls. This reduction in $\dot{V}O2$ peak is a leading cause to greater levels of PEM and related symptoms, thus causing extended periods of recovery time following the maximal CPET, compared to the repeated exercise challenges. It was also identified that many of the participants struggled to maintain a physiological response to exercise that was expected from an exercise test to 60% of peakHR. Although, $\dot{V}O2$, RER, RPE and workload

signalled these individuals were exercising at AT, many individuals had an HR and BP response equivalent to exercising at levels greater than 70% of APMHR.

6.3 Maximal Exercise Test Findings

There are many physiological aspects that require analysis when it comes to determining the effects of exercise on an individual. $\dot{V}O_2$ is a crucial physiological aspect used within exercise testing to analyse an individual's physiological response to exercise stress and was closely analysed for this study. $\dot{V}O_2$ provides a figurative representation for cardiopulmonary fitness, with the margin for decreased $\dot{V}O_2$ max being, if less than 85% of predicted is reached when the body is put under enough stress for greater levels to be reached (Milani et al., 2006). This becomes a crucial measure to analyse ones aerobic capacity and is important particularly with populations where this is impacted, such as ME/CFS. Within this study it was established that the mean $\dot{V}O_2$ peak was 23.36ml·kg·min^{-1}, which is considered low relative to the predicted $\dot{V}O_2$ peak of age/sex matched healthy, sedentary populations (Vermeulen & Vermeulen van Eck, 2014). A further meta-analysis and systematic review on the peak oxygen uptake of those with ME/CFS during exercise suggests that reduced physical activity is directly associated with a reduction in $\dot{V}O_2$ (Franklin et al., 2019). Vermeulen & Vermeulen van Eck, (2014), found that during a maximal exercise test, healthy female individuals had a $\dot{V}O_2$ peak of 27.4ml.kg.min and males a value of 27.3ml.kg.min, compared to that of participants with ME/CFS, where females had a mean $\dot{V}O_2$ peak of 20.3ml.kg.min and males 24.0ml.kg.min. This then suggests that our study aligns with that of previous work examining peak $\dot{V}O_2$ of those with ME/CFS, with a similar low distribution $\dot{V}O_2$ peak being evident.

Those with ME/CFS tend to have a greater exercise intolerance, which could be due to lowered oxygen uptake by muscle cells, and thus combined with a higher increase of cardiac output (relative to oxygen uptake), leading to greater amounts of intolerance (Vermeulen & Vermeulen van Eck, 2014). This lack of tolerance to maximal exercise may be caused by the premature anaerobiosis experienced by those with ME/CFS, which ultimately leads to the reduced ability of aerobic exertion and subsequently causes premature fatigue and overall a lower $\dot{V}O_2$ (Stevens et al., 2018). To reiterate, the reduction of $\dot{V}O_2$ peak in those with ME/CFS during maximal exercise is not necessarily linked to deconditioning. Rather it is considered to be a physiological intolerance to exercise due to the overall reduction of physical activity within an individual's lifestyle, which is supported by several other studies (Franklin et al., 2019; Vermeulen & Vermeulen van Eck, 2014; Stevens et al., 2018; Hodges et al., 2020).

Blood pressure and heart rate are often monitored during exercise. Whilst heart rate provides an indication of cardiovascular response to exercise (Almedia et al., 2019), blood pressure provides information about the physiological system with excessive rises in submaximal exercise BP being associated with adverse cardiovascular events and mortality (Sharman and LaGerche, 2015). Both BP and HR were major characteristics analysed to assess exertion during the maximal CPET. Previous research has suggested that in healthy populations there is a linear relationship between $\dot{V}$O2, workload and HR and BP, with the main characteristic being a gradual increase in BP and HR that is relative to the workload and peak $\dot{V}O_2$ (Sabbahi et al., 2017; Wielemborek-Musial et al., 2016). Both BP and HR increase during exercise to provide adequate blood supply to working muscles, but typically this increase is proportional to the exercise intensity (workload) (Tuka et al., 2015). This study found that relative to $\dot{V}O_2$ peak (mean 23.36 ml·kg·min^{-1}) and workload (mean 131W) of all participants, BP and HR were generally high, with a mean SBP of 169mmHg, mean DBP of 97mmHg and a mean HR of 155bpm. Thus suggesting that the BP and HR response to the $\dot{V}O_2$ peak and workload of this population, is not always the typical linear pattern that is expected from healthy populations completing similar testing. Within this study, some individuals experienced more drastic increases in BP and HR relative to workload than others, with the most notable relationship being an individual with a BP of 240/120mmHg, an HR of 151bpm with a $\dot{V}O_2$ peak of 12.38 ml·kg·min^{-1} and a workload of 45W. Other individuals displayed a relatively normal trajectory when it came to the relationship between these factors, although from the means highlighted, there was a notable skew from what is expected compared to healthy individuals. Ultimately this somewhat abnormal response to maximal exercise, may suggest that within this population, cardiovascular systems are being put under considerable stress, despite the low levels of workload that are being reached, thus causing abnormal HR and BP responses relative to the workload.

Age predicted max heart rate is commonly used for providing a criterion for achieving maximal exertion and is calculated based on someone's age using the equation 220-age (Tanaka, Monahan and Seals, 2001). APMHR was used within this study to provide a target peakHR during the maximal exercise test. However, as previously suggested, within this study individuals struggled to reach an HR response that was relative to the workload they were exerting to. Just one participant within this study was able to reach their calculated APMHR during the maximal CPET. It has been established that there is an underlying issue causing the inability of individuals to reach the predicted max HR, even when provided with an opportunity

to do, so based on workload and $\dot{V}O_2$ peak. Recent research conducted by Davenport et al., (2019), suggests that an overlooked determinant of ME/CFS is Chronotropic Intolerance (CI). CI has long been a determinant of ME/CFS and reflects the inability of individuals to appropriately increase cardiac output despite the stress the body is under (Davenport et al., 2019). CI is broadly defined as the inability for one's heart rate to increase commensurate with increased demand placed on the body, thus leading to a level of exercise intolerance (Brubaker and Kitzman, 2012). CI is identified by varying criteria, including the failure of one to achieve APMHR, when the body is under enough stress to reach this level, along with inadequate heart rate and blood pressure responses proportionate to workload, (Davenport et al., et al., 2019). As mentioned just one participant from this study was able to reach APMHR during the maximal CPET, which again highlights the fact that those with ME/CFS have an interesting cardiovascular response to exercise. The cardiovascular response to exercise in those with ME/CFS is still a very immature area of this condition, with many grey areas still being. apparent, particularly regarding CI. CI is also an aspect of the physiological response to exercise experienced by those with ME/CFS that is considered under researched, but has recently been suggested to be an apparent facet of ME/CFS (Davenport et al., 2019; Wirth and Scheibenbogen, 2020). This being said, this is an area of ME/CFS that should be investigated further to establish the relationship between ME/CFS and exercise intolerance.

6.4 Repeated Exercise Challenge Findings

Repeated exercise challenges have been conducted in various studies examining exercise capacity and recovery in ME/CFS populations (Keller, Pryor and Giloteaux, 2014; Hodges, Nielsen and Baken, 2018; Snell et al., 2013). With the purpose of this study being to investigate the physiological effects of repeated exercise at anaerobic threshold, a repeated exercise challenge design was used, which also aligned with other research that has been conducted within this area (Hodges, Nielsen and Baken, 2018). The repeated exercise challenge, 24-hours apart method was used in this instance, to analyse whether or not performing submaximal exercise to AT could be utilised as an exercise prescription guideline for this population. Once the data was analysed, it was highlighted that there was a drop in mean $\dot{V}O2$, with the mean for first of the repeated exercise challenges being 18.7 $ml{\cdot}kg{\cdot}min^{-1}$, followed the next day with a mean of 16.01$ml{\cdot}kg{\cdot}min^{-1}$, suggesting that a refractory period may be highlighted within this population. This decrease in oxygen consumption between the tests aligns with research conducted by others, where a decrease in peak oxygen consumption at AT was signified (Vermeulen and Vermeulen van Eck, 2014; Keller, Pryor and Giloteaux, 2014). A significant difference between these suggested studies and the one we have completed is that these studies

utilised a ramp style CPET, with workload increasing periodically during the test, compared to this study, where participants cycled at a pre-determined workload (calculated from their maximal CPET) for the duration of the 5-minute test. This allowed the establishment of whether or not frequent/reoccurring exertion at AT was beneficial to this population. With the $\dot{V}O2$ decreasing during the repeated exercise challenge, and the workload remaining the same, this enlightens us that repeated exercise to AT may actually be beneficial to this population. This provides new information surrounding the idea that completing frequent exercise at a reduced intensity, enables individuals to become used to the intensity, thus meaning PEM does not affect the intensity of exertion.

The repeated exercise challenge at AT was a crucial aspect of this study to further assess the timeline of PEM and also to analyse whether current exercise prescription recommendations are valid and successful. To date, research has concluded that exercising to AT reduces the deterioration of physical functioning, with a study conducted by Davenport et al., (2010), suggesting that current guidelines around graded exercise therapy, involve individuals performing frequent exercise at intensities greater than AT, where patients have reported a deterioration of physical functioning. These recommendations are in place due to the direct relationship between heart rate and anaerobic threshold (Aunola and Rusko, 1984). Heart rate at AT has been advocated as a guide with the intention of people avoiding ineffective anaerobic metabolism which occurs once AT has been surpassed (Van Campen, Rowe and Visser, 2020). In 2007 NICE guidelines recommended graded exercise therapy as a form of treatment for ME/CFS and related symptoms. These guidelines suggested individuals should complete 5 to 30 minutes of aerobic exercise aiming for a heart rate of 50-70% of APMHR. However, these guidelines have become under scrutiny recently upon review of the recommendations, due to the complexity of ME/CFS and the varying symptoms and degree of symptoms experienced by each individual. When $\dot{V}O_2$, RER and RPE are analysed it is viable to suggest that all individuals are working within the recommended target range for AT, yet 6 of the 11 participants have an HR response equivalent to exercising >84% of their peak HR from the initial max CPET and 4 of the 11 participants, increasing their heart rate beyond the 70% threshold based on their percentage of APMHR, despite having a significantly lower workload and taking less time to recover, compared to the remaining 7 participants. It can also be acknowledged that this group had a higher $\dot{V}O2$ during the first exercise challenge, yet had a much lower $\dot{V}O2$ during the repeated exercise challenge. The remaining 7 participants were able to increase their HR to within the recommended AT range whilst maintaining a similar

$\dot{V}O2$ for both tests. This information highlights once again, the idea that some individuals with ME/CFS are unable to maintain an expected response to repeated exercise, thus justifying the notion that surrounds the complexity of exercise prescription and broader treatments for this population.

Torjesen (2020), reviewed the current NICE recommendations, by suggesting that due to the complex, multi-system nature of this chronic medical condition, there is no place for a "one size fits all" approach, hence the exclusion from updated guidelines for Exercise Prescription. Instead individuals should remain within their energy limits when partaking in any form of exertion, with emphasis being placed on the fact that each individual experiences a fluctuating energy limit and it is more beneficial for individuals to base their exertion off their own limits. Nevertheless, these new recommendations don't help when it comes to exercise prescription as a treatment for those with ME/CFS. Research from our current study has previously suggested that even at low levels of exercise (45 watts), many cannot maintain a heart rate between the originally suggested 50-70% APMHR, and in fact their cardiovascular system is working considerably harder. As mentioned previously just 4 of the 11 participants were able to maintain an HR response at low intensities within this range. Therefore suggesting that exercise may not be the best form of treatment for the other 7 participants, as their cardiovascular system is unable to respond to the demand and is put under undue stress. From this, it may also be postulated that everyday activities may also be putting individuals cardiovascular system under significant stress, thus suggesting that the cardiovascular response to exertion is an area of this condition that should be investigated further.

6.5 HRV Findings

HRV was assessed in this study to gain a basic understanding of normalities for those with ME/CFS. As suggested there are no significant changes to the HRV findings over the course of the three tests. When results of this study are compared to that of previous studies conducted, the results are as to be expected, with an overall lower HRV but a higher resting heart rate (RHR), compared to 'healthy' control populations (Hansen et al., 2012) (Nelson et al., 2019). HRV provides a monitoring tool for the adaption of the heart to physical activity (Dong, 2016), and although the general findings of this study suggest HRV in the ME/CFS population is slightly different to that of the general population, when it comes to HRV response to exercise (analysed from the difference between tests 2 and 3), most of the determinants see a 'normal' response to exercise (Dong, 2016). When we compare the results of the previously explained Group 1 and 2 in this study, there were no significant differences between the two groups, even

though Group 2 were physiologically working harder during the repeated exercise challenges. This then suggests, that the HRV response of this population over the course of the three tests is fairly normal, with further research being required in order to assess whether there is a difference in HRV response to exercise within this population over a greater duration of time, compared to 'healthy' control populations.

6.6 Cognitive (Neuropsychological) Test Findings

It has previously been established that a decline in cognitive functioning is associated significantly with ME/CFS. However, it has also been recognised that physical exercise can affect brain plasticity, thus promoting improved cognition and wellbeing (Weinberg and Gould, 2015). Physical exercise has been proven to induce important structural and functional changes within the functioning of the brain, such as increased blood flow, improved cognitive abilities (learning, memory and attentional processes) and prevention of cognitive decline (leading to dementia in elderly) (Mandolesi et al., 2018). Over the course of the three occasions, the participants completed the cognitive tests, assessing areas of memory, concentration, recall, and reaction time. Results gradually improved, with significant improvements seen in recall testing and overall completion time. P-values of the recall number 1 and 2 tests (0.001 and 0.003 respectively), and the overall completion time (P-Value of 0.015), between the repeated exercise tests, suggest that repeated exercise to AT does not provoke detrimental effects on aspects of cognitive function in those with ME/CFS. Even though those with ME/CFS often experience reduced cognitive performances, cognitive functioning is an aspect that can improve when it is consistently practiced (Johnson et al., 1997), Thus, suggesting that cognition is often considered to be a 'learnt' activity, with participants completing the exact same test three times, the 'practice effect' is highlighted, leading to a degree of improvement across the trials (Johnson et al., 1997). When highlighting the fact that these improvements are minimal across the trials, it has previously been suggested that those with ME/CFS often experience improvements in cognition at a much slower rate, compared to 'healthy' counterparts (LaManca et al., 1998). Though cognitive testing was not the primary purpose of conducting this study, it was intriguing to identify that exercise 24-hours prior to completing the neuropsychological testing did not seem to inhibit the cognitive outcomes the following day and in fact, may have enhanced the cognitive ability of participants to complete the testing. It was also interesting to identify that when the pool of participants were split into the previously mentioned two groups, even though Group Two were working at a greater physiological capacity, their cognitive testing results did not differ significantly to that of Group One who were not physiologically exerting to the same capacity, which provides another

good opportunity for future research in this area of ME/CFS. If the results are analysed the other way and it is suggested that due to the cognitive tests being a 'learnt' activity, greater improvements are expected to be seen, the more the tests are completed. One study suggests that during the early phases of high-frequency repeated cognitive tests, practice effects are prominent (Bartels et al., 2010). Thus providing a basis for argument and further research, as to whether the lack of change in cognition during the early stages of testing is a 'normal' response.

6.7 Subjective Measures of Fatigue

Subjective measures within this area of study are important for providing information on the PEM timeline and for identifying recovery durations for those with ME/CFS. The subjective measures utilised in this study, aligned with previous research completed by Hodges, Nielsen, and Baken, (2018), who utilised the same method. In line with previous research conducted, participants took longer to recover following the maximal exercise test, compared to the repeated exercise challenges This difference in recovery days has been considered a significant difference with individuals feeling as though they had recovered from the maximal exercise test in 9.18 days, compared to taking just 5.23 days to recover from the repeated (24-hour) exercise challenges. Thus, aligning with the original hypotheses that suggested individuals with ME/CFS will experience greater amounts of fatigue and take longer to recover following the maximal CPET compared to following the repeated exercise challenges. Research conducted by Hodges, Nielsen and Baken (2018), highlighted that due to those with ME/CFS taking longer to recover, the more days between bouts of exercise, the more optimal individuals will be able to perform during exertion. It is considered normal to recover at a quicker rate when exercise is consistent and at a lower intensity due to the physiological adaptions accumulated after consistent bouts of acute exercise, which is often referred to as the exercise training response (Cornelissen et al., 2010). Thus suggesting that when exercise is prescribed to those with ME/CFS, exercise bouts should not be prescribed on consecutive days to reduce the PEM timeline and provide greater time for recovery. Most healthy individuals would be recovered within 24-hours following submaximal aerobic exercise, however the findings from this study demonstrate that this is not the case for those with ME/CFS. Thus, suggesting that lowered intensity and duration exercise on consecutive days is not necessarily beneficial for the ME/CFS population and highlighting guidelines surrounding this should be a priority for future research.

6.8 Limitations

When researching those with ME/CFS, it came to our attention that it is very clear there is a diverse range of fatigue levels on any given day amongst this population. There is a great fluctuation of severity of fatigue within this population and also within individuals personally on a day-to-day basis. To ensure the varying degrees of fatigue didn't alter ability of performance during testing for the individuals, we implemented a consistent recruitment process for all participants and ensured that all testing protocols were maintained for every participant to ensure all participants underwent the same processes. To reduce the level of variation regarding the individual day-to-day fatigue experienced by participants, we asked each individual to continue completing normal day-to-day tasks and to aim to not change their daily routine. This ensured no external factors altered the outcome of the research too much.

As mentioned above, only 11 participants partook in this study. A significant factor as to why this was, was due to the complexity and difficulty of recruiting participants. We found that a lot of individuals were not eager to participate due to the demand the testing placed on their body. We originally suggested we would be aiming to recruit 20 participants, but due to the difficulty of recruiting participants, just 11 individuals meet the required criteria to participate in the study. All participants were made aware of the impacts that testing could have on their fatigue and fatigue related symptoms, and sometimes this was to the detriment of the study where participants would choose not to participate.

I would also like to acknowledge that due to the pandemic Covid-19 (Coronavirus), that struck worldwide in March/April 2020, we had to put data collection on hold. Fortunately, we had already collected half of the data required for this research meaning this thesis has been completed based on the already collected data. However, this may result in the research for this particular thesis being underpowered, with further data collection needing to be completed to establish a well-developed and powered research argument.

The final limitation that needs to be acknowledged is that most of the participants were above the age of 40, with just one of the participants being under this age (28). This is considered a limitation as it means the spread of age is a lot greater. With the eldest participant being 64 and the youngest being 28, and the other nine individuals spread between, the overall spread of the data will be greater. Ideally it would be better to either increase or to gain participants within a tighter age band for future research.

6.9 Recommendations for Future Research

Based on the findings of this study, additional research is required to investigate and be able to understand why those with ME/CFS physiologically respond to exercise differently compared to 'healthy' populations. Particular focus on BP, HR and RER response to submaximal repeated exercise would provide a greater understanding of reasons behind the reduced level of exercise capacity, thus providing more information for prescribing exercise to the ME/CFS population. This study was able to identify some interesting details surrounding physiological response to submaximal exercise experienced in this population, and recovery times from such exercise, however, to understand the condition further, research that focuses on these responses would provide more clinically based considerations when prescribing exercise to these individuals. Furthermore, based on the identification of APMHR not necessarily being an adequate baseline for exercise prescription, greater research could be done on other methods of exercise prescription, with the aim of trying to identify a more accurate means of target markers. Further research on the PEM timeline may be required to ensure individuals are provided adequate recovery time between bouts of exercise, to ensure symptoms of fatigue are not exacerbated by exercise.

Regarding cognitive functioning of those with ME/CFS, it would be informative to provide greater amounts of reliable findings on whether consistent exercise improves overall cognitive functioning, particularly in areas that are significantly impacted by fatigue such as memory, concentration and general 'brain fog'.

CHAPTER SEVEN: CONCLUSIONS

The purpose of this study was to identify the physiological and cognitive effects of a repeated 5-minute exercise challenge experienced by individuals with ME/CFS. Areas of particular interest were physiological variables such as HR, BP, $\dot{V}O2$, , RER and RPE, along with other variables such as PEM, HRV and cognitive functioning. Through analysing all of the said variables, it was hoped that safe and beneficial exercise guidelines could be developed for the ME/CFS population.

This study identified some intriguing information regarding physiological response to exercise in those with ME/CFS, particularly surrounding BP and HR response to submaximal exercise. It needs to be acknowledged that given the mean workload and mean $\dot{V}O_2$ that participants were exercising at, the BP and HR response was out of character, thus suggesting that this is an area that would need more investigation to highlight why this response was apparent. The findings suggest that using APMHR for those with ME/CFS is not a safe prescription method and rather actual %HRmax based on a cardiopulmonary exercise test, would be a safer option due to the complexity and variety among individuals with ME/CFS. Every individual with ME/CFS has varying symptoms and varying degree of symptoms, thus suggesting that looking at exercise prescription on a 'case-by-case' basis is going to be more beneficial for this population. Subjective results of the study found that completing just 5 minutes of exercise to AT, repeated 24 hours later a mean of 5 days was required to recover, compared to the mean of 9 days following the maximal CPET exercise test. This provides new details that can be taken into consideration when exercise is prescribed to the ME/CFS population, with the key factor for consideration being that those with ME/CFS should not be prescribed exercise on consecutive days and intensity should be reduced compared to 'healthy' counterparts. However, greater research should be conducted on this to establish concrete evidence surrounding a timeline.

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CHAPTER NINE: APPENDICIES

9.1 Participant Information Sheet and Consent Form

MASSEY UNIVERSITY
School of Sport, Exercise and Nutrition
Private Bag 11 222
Palmerston North
New Zealand
Telephone: 64 6 350 4336
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PARTICIPANT INFORMATION SHEET

Study title:	*The effects of graded exercise till anaerobic threshold on post exertional malaise in individuals with CFS/ME*		
Locality:	**Massey University, Palmerston North**	Ethics committee ref.:	
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 produce evidence-based research to provide safe exercise guidelines to help with the treatment and management of CFS/ME. In this study we will look at the effect of graded exercise and its effects on the heart and lungs, your ability to complete tasks and your levels of fatigue. It is hoped that this will allow us to understand if there is an

exercise intensity for individuals to exercise at without feeling like they can't do anything in the days following.
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. The study is currently being approved by the Health and Disabilities Ethics Committee

WHAT WILL MY PARTICIPATION IN THE STUDY INVOLVE?

You have been identified for the study because you have symptoms of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. You may be Maori or European.

All participants will be asked to complete an online version of the De Paul Symptom Questionnaire, as well as a Physical Activity Readiness Questionnaire. This will be analysed to ensure that participants meet the CFS International, Canadian and Fukuda criteria for diagnosis of ME/CFS.

All individuals will visit the Human Performance Lab, at Massey University Palmerston North.

Pre-Exercise Measures

- *You will have 3 visits to the Palmerston North Human Performance Lab.*
- *Prior to your first and third visit, you will complete a 7-day daily diary of fatigue.*
- *On your first visit to the Human Performance Lab, you will have your resting blood pressure, height and weight recorded.*
- *You will then have the stiffness of your arteries measured by a tonometer which looks at the pressure at your carotid and radial artery.*
- *You will then be asked to wear a heart rate monitor and asked to put your index finger over the camera of a phone where by individuals will have their heart rate variability recorded whilst standing and lying down for 5 minutes in each position.*
- *You will be asked to complete a series of computer tests to help us understand how quickly and correctly you can process information. This will provide us with information on attention, learning and memory.*
- *Lastly you will complete an incremental cycle ergometer exercise test. During the test, you will exercise at progressively harder intensities until you reach volitional exhaustion (where you can no longer continue). This will be generally about 4-8 minutes of activity. This will tell us about your heart and your 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 wear a nose clip and a mouthpiece, so that we can collect breath by breath gas samples throughout the exercise test. Every participant will complete a standard cool down procedure where heart rate and blood pressure will be measured during the 5-minute period.*
- *On completion of the exercise test you will be asked some questions about how you are feeling. Testing on each occasion should take no more than an hour and a half of your time. The purpose of the questionnaires are to quantify and clarify different types of fatigue and how they relate to health and well-being and also to assess how long it takes for each group to fully recover from the exercise testing.*
- *You will complete a 10-day daily diary of fatigue.*

- *You will be asked to come back to the lab 1-2 months later where we will complete the same tests again, 24 hours apart, but we will only exercise to approximately 60% of your initial workload across both days.*

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, and feeling more fatigued than usual for up to 4 weeks following the exercise tests.

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.

In the event of a medical emergency, whilst laboratory personnel are trained in basic life support procedure, the local ambulance service will be summoned in the usual way. The human performance lab has a defibrillator and all staff are trained in its use. All researchers have current first aid at work qualifications.

Benefits

The results obtained in this study will be used to develop a method for evaluating whether an individual can exercise below the anaerobic threshold without showing physical and cognitive signs of post exertional malaise. It is anticipated that this study will help provide information on appropriate levels of exercise which are currently largely unknown within this group of individuals.

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?

Briefly explain:

- *the voluntary nature of participation, including that they are free to decline to participate, or to withdraw from the research at any practicable time, without experiencing any disadvantage*
- *that participants have the right to access information about them collected as part of the study*
- *that participants will be told 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*
- *what provision will be made for the privacy and confidentiality of individuals*

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

Participants from the current study may be contacted for further research studies following on from this study examining exercise and post exertional malaise but would need to complete a further participant consent form to take part in any future research.
Study data will be stored for in a locked filing cabinet and a password protected computer for 10 years. After 10 years, 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, Exercise and Nutrition
Private Bag 11 222
Palmerston North
New Zealand
Telephone: 64 6 350 4336
Facsimile: 64 6 350 5657

INFORMED CONSENT FORM

If you need an INTERPRETER, please tell us.

Please tick to indicate your consent to the following

1.	I have read or have had read to me in my first language, and I understand the Participant Information Sheet.	Yes ☐	No ☐
2.	I have been given sufficient time to consider whether or not to participate in this study.	Yes ☐	No ☐
3.	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 ☐
4.	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 ☐
5.	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 ☐
6.	I consent to the research staff collecting and processing my information, including information about my health.	Yes ☐	No ☐
7.	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 ☐
8.	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 ☐
9.	I understand that there may be risks associated with the treatment.	Yes ☐	No ☐
10.	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 ☐
11.	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 ☐
12.	I understand the compensation provisions in case of injury during the study.	Yes ☐	No ☐

13. I know who to contact if I have any questions about the study in general. Yes ☐ No ☐
14. I understand my responsibilities as a study participant. Yes ☐ No ☐
15. 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 Fatigue Diary

(7-days given prior to testing; 10-days given post testing)

Daily diary of fatigue symptoms

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

EXERCISE RECOVERY QUESTIONS

WELL ME

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?
   _____
   Comments:_____
   _____
   _

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