

Validity of 2-Day Cardiopulmonary Exercise Testing in Male Patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

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How to cite this paper: van Campen, C. M. C., Rowe, P. C., & Visser, F. C. (2020). Validity of 2-Day Cardiopulmonary Exercise Testing in Male Patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Advances in Physical Education*, 10, 68-80. <https://doi.org/10.4236/ape.2020.101007>

Received: January 30, 2020

Accepted: February 18, 2020

Published: February 21, 2020

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Abstract

Introduction: Among the main characteristics of patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) are effort intolerance along with a prolonged recovery from exercise and post-exertional exacerbation of ME/CFS symptoms. The gold standard for measuring the severity of physical activity intolerance is cardiopulmonary exercise testing (CPET). Multiple studies have shown that peak oxygen consumption is reduced in the majority of ME/CFS patients. A consecutive day CPET protocol has shown a difference on day 2 in ME/CFS patients in contrast to sedentary controls. Because of the low number of male ME/CFS patients in the published literature, and because of a possible gender difference in the clinical phenotype, the aim of this study was to examine whether the response to a 2-day CPET protocol in a larger sample of male ME/CFS patients was similar to that observed in females. **Methods:** From 77 male patients, 25 male ME/CFS patients fulfilled the criteria of a 2-day CPET protocol for analysis. Measures of oxygen consumption (VO_2), heart rate (HR), systolic and diastolic blood pressure, workload (Work), and respiratory exchange ratio (RER) were made at maximal (peak) and ventilatory threshold (VT) intensities. Data were analysed using a paired t-test. **Results:** Baseline characteristics of the group were as follows. Mean age was 44 (12) years, mean BMI was 27.1 (4.4) kg/m^2 . Median disease duration was 10 years (IQR 7 - 13). Heart rate, systolic and diastolic blood pressure at rest and the RER did not differ significantly between CPET 1 and CPET 2. All other CPET parameters at the ventilatory threshold and maximum exercise differed significantly (p -value between <0.005 and <0.0001). All patients experienced a deterioration of performance on CPET2 as measured by the predicted and actual VO_2 and workload at peak exercise and ventilatory threshold. **Conclusion:** This study confirms that male ME/CFS pa-

tients have a reduction in exercise capacity in response to a consecutive day CPET. These results are similar to published results in female ME/CFS populations.

Keywords

Chronic Fatigue Syndrome, Cardiopulmonary Exercise Testing, VO₂ Peak, Ventilatory Threshold, VO₂ AT, RER, Myalgic Encephalitis, Workload

1. Introduction

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a serious and potentially disabling chronic disease (Carruthers et al., 2011; Clayton, 2015; Fukuda et al., 1994; IOM, 2015). The exact pathophysiology has not been established but there is considerable evidence that ME/CFS is associated with abnormalities of the central and autonomic nervous systems, and that an association with infectious agents and immunological abnormalities is often present (Arnett et al., 2011; Gerrity et al., 2004; Gur & Oktayoglu, 2008; Klimas et al., 1990; Komaroff & Cho, 2011; Naess et al., 2010; Okamoto et al., 2012; Ortega-Hernandez & Shoenfeld, 2009; Stewart, 2000). Abnormalities of energy metabolism also have been described (Fluge et al., 2016; Naviaux et al., 2016; Tomas et al., 2018; Wong et al., 1992).

One of the main characteristics of patients with ME/CFS is effort intolerance along with a prolonged recovery from exercise and post-exertional exacerbation of ME/CFS symptoms (IOM, 2015), termed post-exertional malaise (PEM) (Jones et al., 2010; Paul et al., 1999). The pathophysiology of the exercise intolerance is not exactly known but involves both metabolic abnormalities of skeletal muscles as well as central nervous system abnormalities (Fulle et al., 2007; Gur & Oktayoglu, 2008; Jones et al., 2010; McCully et al., 2006; McCully et al., 2003; Siemionow et al., 2004; Wong et al., 1992).

The gold standard for measuring the severity of physical activity intolerance is cardiopulmonary exercise testing (CPET). Multiple studies have shown that peak oxygen consumption is reduced in the majority of ME/CFS patients (De Becker et al., 2000; Fulcher & White, 2000; Hodges et al., 2018; Jammes et al., 2005; Keller et al., 2014; Sargent et al., 2002; Sisto et al., 1996; Snell et al., 2013; Vanness et al., 2007; Vermeulen et al., 2010; Vermeulen & Vermeulen van Eck, 2014; Wallman et al., 2004). However, studies have also shown that a single CPET may show in ME/CFS patients that peak VO₂ values can be similar to or only slightly lower than those of healthy sedentary controls. A 2-day CPET protocol, with two CPET separated by 24 hours has confirmed that ME/CFS patients have significantly lower VO₂ and workload parameters on day 2 (CPET 2) than on day 1 (CPET 1). In contrast, sedentary controls have unaltered or slightly improved VO₂ and workload (Keller et al., 2014; Lien et al., 2019; Nelson et al., 2019; Snell et al., 2013; Vanness et al., 2007; Vermeulen et al., 2010).

The CPET studies published thus far have primarily enrolled women. Some of the studies have included only females (Snell et al., 2013; Vermeulen et al., 2010) and those that have enrolled both males and females have included very few males—5 and 7 respectively (Keller et al., 2014; Nelson et al., 2019).

CPET values of males and females differ due to a variety of factors, including weight, height, total body fat, total muscle mass, haemoglobin, cardiac volumes, and lung volumes (Cureton et al., 1986; Fletcher et al., 2001; Fomin et al., 2012; Higginbotham et al., 1984; Sharma & Kailashiya, 2016; Wheatley et al., 2014). Because of the low number of male ME/CFS patients studied and because of a possible gender difference in the clinical phenotype (Faro et al., 2016), the aim of this study was to examine the effect of a 2-day CPET protocol in male ME/CFS patients.

2. Patients, Material and Methods

Eligible participants were males with ME/CFS and exercise intolerance who had been referred to the Stichting CardioZorg, a cardiology clinic in the Netherlands that specializes in diagnosing and treating adults with ME/CFS. All patients underwent a detailed clinical history to establish the diagnosis of ME/CFS according to the ME criteria (Carruthers et al., 2011) and CFS criteria of Fukuda (Fukuda et al., 1994). We reviewed the clinical records of the 77 male patients who had a CPET between June 2012 and October 2017. Four were excluded because the ventilatory threshold could not be accurately be determined, 11 were excluded because they did not fulfill the criteria of ME/CFS, 34 had only a single CPET, and 3 patients had more than one test, but not on 2 consecutive days. This left 25 male patients with data from a 2-day CPET protocol available for analysis. In all patients alternative diagnoses which could explain the fatigue and other symptoms were ruled out. No alternative diseases that could explain the ME/CFS symptoms were identified.

All patients give informed consent to analyze their data. The use of clinical data for descriptive studies was approved by the ethics committee of the Slotervaart Hospital, the Netherlands (reference number P1736).

Cardiopulmonary exercise testing (CPET)

Patients underwent a symptom-limited exercise test on a cycle ergometer (Excalibur, Lode, Groningen, the Netherlands) according to a previously described protocol (Vermeulen & Vermeulen van Eck, 2014). A RAMP workload protocol was used varying between 10 - 30 Watt/min increases, depending on sex, age, and expected exercise intolerance. Oxygen consumption (VO_2), carbon dioxide release (VCO_2), and oxygen saturation were continuously measured (Cortex, Procure, The Netherlands), and displayed on screen using Metasoft software (Cortex, Biophysic GmbH, Germany). An ECG was continuously recorded and blood pressures were measured continuously using the Nexfin device (BMEYE, Amsterdam, The Netherlands) (Martina et al., 2012). Cycle seat height was positioned to approximately 175° of knee extension, and the same seat height was used for both tests. Expired gases were collected breath-by-breath through a two-way breathing valve, and analyzed using open circuit spirometry.

The metabolic measurement system (Cortex, Biophysic GmbH, Germany) was calibrated before each test with ambient air, standard gases of known concentrations, and a 3-L calibration syringe. The ventilatory threshold (VT), a measure of the anaerobic threshold, was identified from expired gases using the V-Slope algorithm (Beaver et al., 1986). Ventilatory or anaerobic threshold is the exercise intensity at which metabolism transitions toward increased anaerobic energy production. The same experienced cardiologist supervised the test and performed visual assessment and confirmation of the algorithm-derived VT. Testing took place in a controlled environment with a temperature range of 20°C - 24°C and 15% - 60% relative humidity. Patients were encouraged by standard phrases each minute to perform maximally to the point of exhaustion. The mean of the VO_2 measurements of the last 15 seconds before ending the exercise (peak VO_2) was taken. VO_2 at the peak and at the VT as well as the heart rate (HR) at the peak exercise were expressed as a percentage of the normal values of a population study: %peak VO_2 , %VT VO_2 and %peak HR (Glaser et al., 2010). Also the mean respiratory exchange ratio (RER; VCO_2/VO_2) of the last 15 seconds was calculated. Immediately after the test the attending cardiologist noted the primary reason for termination the exercise.

Statistical analysis

Data were analyzed using the statistical package of Graphpad Prism version 6.05 (Graphpad software, La Jolla, California, USA). All continuous data were tested for normal distribution using the D'Agostino-Pearson omnibus normality test, and presented as mean (SD) or as median with the IQR, where appropriate. Because of the multiple comparisons a conservative p value of <0.01 was considered significantly different.

3. Results

Table 1 shows the characteristics of the study participants. Mean age was 44 (12) years, median BMI was 27.1 (4.4) kg/m^2 . Median disease duration was 10 years (IQR 7 - 13). According to the ICC criteria, 14 patients had mild disease, 10 patients had moderate disease and one patient had severe disease.

Table 2 shows the parameters of the CPET of day 1 and day 2 and the percent decline on day 2 compared to day 1. Heart rate, systolic and diastolic blood pressure at rest and the RER did not differ significantly between CPET 1 and CPET 2. All other CPET parameters at the ventilatory threshold and maximum exercise differed significantly. **Figure 1** shows the values of peak VO_2 at CPET1 and CPET2 (panel A), %predicted peak VO_2 at CPET1 and CPET2 (panel C), VO_2 at the ventilatory threshold at CPET1 and CPET2 (panel B) and the %predicted VO_2 at the ventilatory threshold for CPET1 and CPET2 (panel D). All were highly statistically significant different ($p < 0.0001$).

Figure 2 shows the workload graphs at peak exercise for CPET1 and CPET2 (panel A) and at the ventilatory threshold for CPET1 and CPET2 (panel B). The differences between CPET 1 and CPET 2 for both workload parameters were highly significantly different ($p < 0.0001$).

Table 1. Baseline criteria*.

	ME/CFS (n = 25)
Age in years	44 (12)
Height in cm	182 (8)
Weight in kg	89 (14)
BSA in m ²	1.7 (0.2)
BMI in kg/m ²	27.1 (4.4)
Disease duration in years	10 (7-13)

*Values are expressed as mean (SD) or as median with the IQR, where appropriate. Abbreviations: BMI: body mass index (DuBois formula); BSA: body surface area.

Table 2. CPET1 and CPET2 variables for ME/CFS male patients*.

Peak exercise	CPET 1	CPET 2	Range of absolute differences CPET 2-CPET 1	% difference CPET 2-CPET 1	P-value
VO ₂ peak in ml/min/kg	27 (8)	24 (8)	-1 to -6	-10 (5)	<0.0001
%pred VO ₂ peak	76 (21)	69 (20)	-1 to -17	-10 (5)	<0.0001
HR rest in bpm	79 (13)	80 (10)		2 (13)	ns
HR peak in bpm	150 (24)	142 (24)		-5 (4)	<0.0001
%pred HR peak	82 (11)	78 (12)		-5 (5)	<0.0001
SBP rest in mmHg	128 (17)	121 (16)		-5 (11)	ns
SBP peak in mmHg	194 (21)	176 (21)		-9 (10)	=0.0005
DBP rest in mmHg	83 (9)	80 (7)		-3 (11)	ns
DPB peak in mmHg	109 (9)	102 (10)		-6 (8)	<0.005
Workload peak in Watts	206 (55)	187 (51)	-4 to -50	-10 (6)	<0.0001
RER peak	1.1 (0.1)	1.1 (0.1)		-2 (6)	ns
Ventilatory threshold					
VO ₂ VT in ml/min/kg	16 (5)	12 (3)	-1 to -13	-22 (9)	<0.0001
%pred VO ₂ VT	40 (14)	31 (10)	-3 to -36	-22 (9)	<0.0001
HR VT in bpm	111 (14)	99 (12)		-10 (7)	<0.0001
Workload VT in Watts	105 (31)	74 (27)	-2 to -86	-30 (17)	<0.0001

*Values are expressed as mean (SD). Abbreviations: VT: ventilatory threshold; CPET: cardiopulmonary exercise test; DBP: diastolic blood pressure; HR: heart rate; pred: predicted; RER: respiratory exchange ratio; SBP: systolic blood pressure; VO₂: oxygen consumption.

Figure 3 displays the range of absolute difference of 6 CPET parameters: VO₂ peak, predicted %VO₂ peak, VO₂ at the ventilatory threshold, predicted %VO₂ at the ventilatory threshold, workload at the ventilatory threshold and workload at peak exercise. In all patients of this study population values worsened at CPET 2 compared to CPET 1.

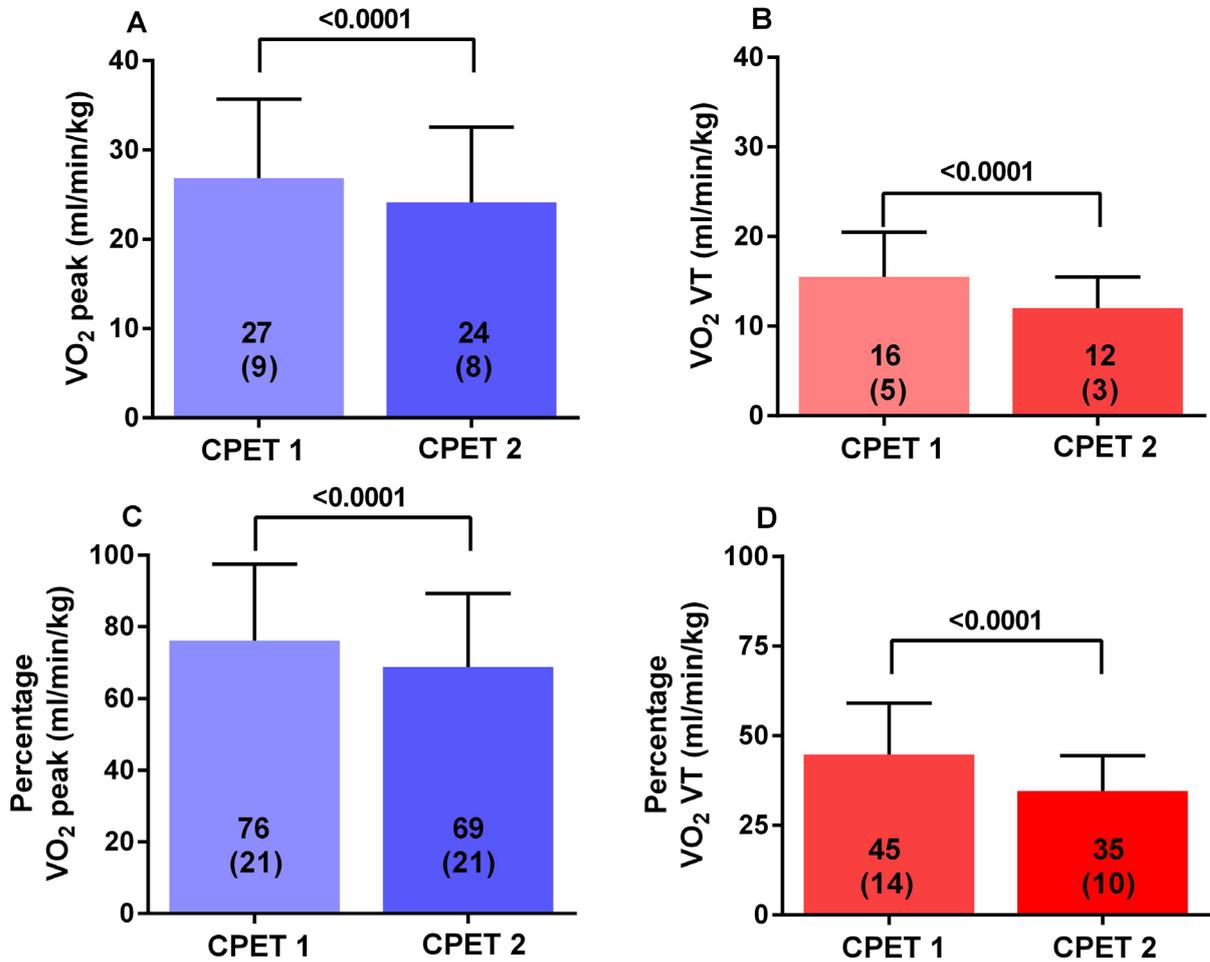


Figure 1. Shows the peak oxygen consumption for CPET1 and CPET2 (panel A), the %predicted peak oxygen consumption for CPET1 and CPET2 (panel B), the oxygen consumption at ventilatory (anaerobic) threshold for CPET1 and CPET2 (Panel C) and the %predicted oxygen consumption at ventilatory threshold for CPET1 and CPET2 (Panel D). CPET: cardiopulmonary exercise test; VT: ventilatory (or anaerobic) threshold.

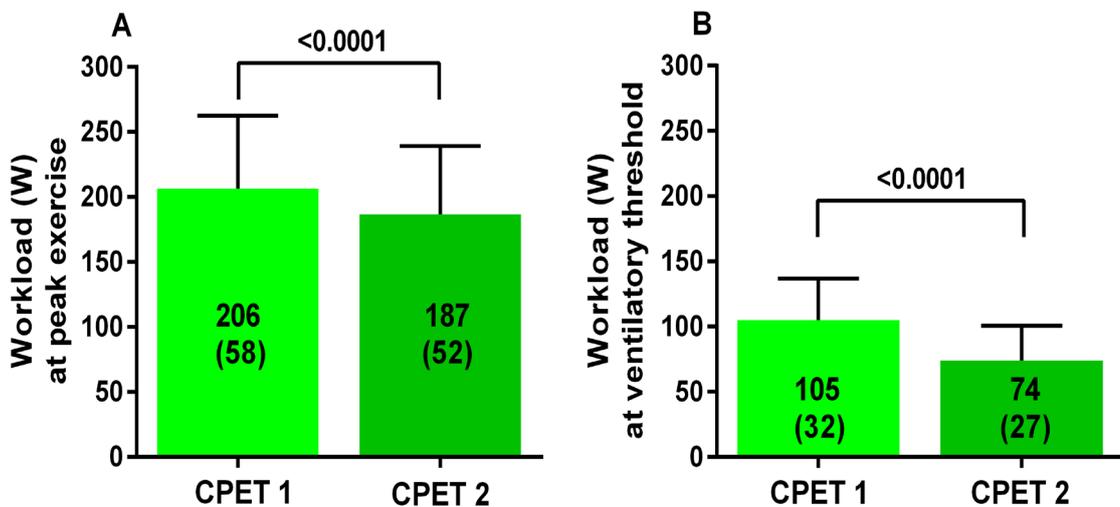


Figure 2. Workload at peak exercise for CPET1 and CPET2 (panel A) and at the ventilatory threshold for CPET1 and CPET2 (panel B). CPET: cardiopulmonary exercise test.

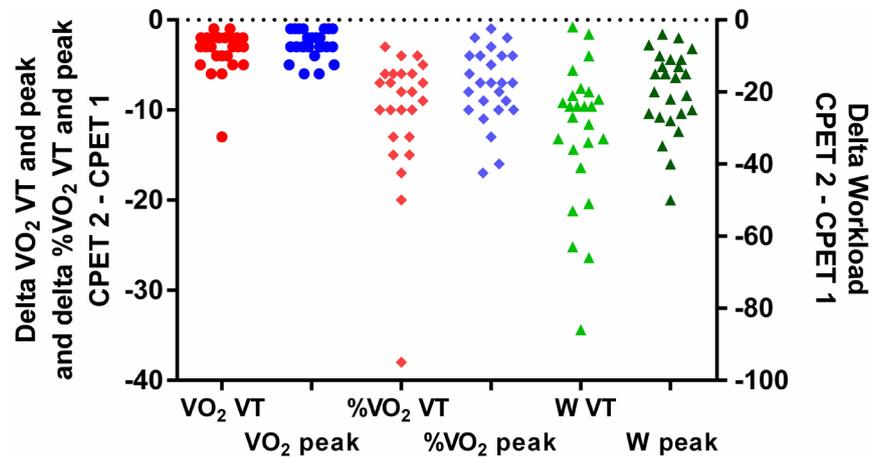


Figure 3. Range of absolute differences of CPET parameters, peak VO_2 , predicted %peak VO_2 , VO_2 at the ventilatory threshold, predicted % VO_2 at the ventilatory threshold, workload at the ventilatory threshold and workload at peak exercise (CPET 2-CPET 1). CPET: cardiopulmonary exercise test; VT: ventilatory (or anaerobic) threshold.

4. Discussion

A two day CPET protocol in ME/CFS patients shows a unique feature of the disease: that the VO_2 peak and at the ventilatory threshold are reduced at the second day which is in contrast to the VO_2 data in sedentary controls (Lien et al., 2019; Nelson et al., 2019; Snell et al., 2013; Vanness et al., 2007; Vermeulen et al., 2010). These findings of the lower VO_2 at peak exercise on the second day in ME/CFS patients, in contrast to sedentary controls, makes it unlikely that this phenomenon is due to deconditioning (Nijs et al., 2004; Vanness et al., 2007), and suggests metabolic abnormalities. The lower peak VO_2 on day two has been referred to as an early sign of post-exertional malaise (PEM) (IOM, 2015).

In studies analyzing the difference between day 1 and day 2 CPET in ME/CFS patients, only 2 studies included a limited number of male patients, 5 and 7 patients respectively (Keller et al., 2014; Nelson et al., 2019). As VO_2 at peak exercise differs between male and females, the inclusion of both genders using peak VO_2 as one of the endpoints has the potential to create a measurement bias (Fomin et al., 2012; Higginbotham et al., 1984). To investigate whether males have a different CPET phenotype, we analyzed the response to CPET in a larger male ME/CFS patient sample. The main finding of this study was that in male ME/CFS patients, all measurements of VO_2 and workload at the ventilatory threshold and at peak exercise were significantly lower on the second day CPET compared to the first day, similar to published findings in females. As over half of our study population would be classified as having mild ME/CFS, and all but one of the remaining participants would be classified as having moderate disease, the decline on day 2 cannot be attributed to having enrolled a more diseased population. Furthermore, systolic and diastolic blood pressures at peak exercise were lower on day 2 compared to day 1, a novel finding not described in the previous studies. Additionally, we also observed a lower heart rate at the ventilatory threshold, apart from lower heart rate at peak exercise on day 2 compared to day 1,

as had been described earlier by Nelson et al. (Nelson et al., 2019).

Cardiopulmonary exercise testing 2-day protocols: comparison to literature

VanNess et al. (Vanness et al., 2007) studied 6 female CFS patients and 6 female sedentary controls in a two day CPET protocol. This study documented a significant decline in VO_2 peak and VO_2 at ventilatory threshold at the second day. Our results in male ME/CFS patients are consistent with these findings. Remarkably, this study showed no difference in VO_2 values between patients and controls at day 1.

Vermeulen et al. (Vermeulen et al., 2010) studied 15 female ME/CFS patients and 15 female controls in a two day CPET protocol. At both day one and day two a significant lower peak VO_2 and VO_2 at the ventilatory threshold was found in ME/CFS patients compared to controls. In ME/CFS patients there was a decrease between day 1 and day 2 in peak VO_2 and an unaltered VO_2 at the ventilatory threshold. For controls an increase in peak VO_2 and VO_2 at the ventilatory threshold was observed at day 2.

Snell et al. (Snell et al., 2013) studied 51 female ME/CFS patients and 10 female controls. Multivariate analysis showed no significant differences between control participants and participants with CFS for test 1. However, for test 2, participants with CFS achieved significantly lower values for oxygen consumption and workload at peak exercise and at the ventilatory or anaerobic threshold. No males were studied.

Keller et al. (Keller et al., 2014) studied 22 CFS patients (17 females and 5 males) in a two day CPET protocol. No controls were included. Peak VO_2 , VO_2 at the ventilatory threshold, peak workload and workload at the ventilatory threshold were all significantly lower at day two. Moreover, the authors related the VO_2 data with a classification of functional impairment (Weber & Janicki, 1985). This classification of functional impairment worsened in 50% of the ME/CFS cohort due to post-exertional decrements in peak VO_2 and/or VO_2 at the ventilatory threshold.

Nelson et al. studied 16 ME/CFS patients (9/7 female/male) and 10 controls (5/5 female/male) (Nelson et al., 2019). The largest change reported in this study was a decline in workload at the ventilatory threshold. Decreases in maximal workload, peak VO_2 , and VO_2 at the ventilatory threshold were non-significant between controls and ME/CFS patients and between day one and day two tests. They concluded that decrease of the workload at the ventilatory threshold in ME/CFS patients may represent an objective biomarker for the diagnosis of ME/CFS.

Finally, Lien et al. included ME/CFS patients and controls: 18 patients and 15 controls completed the total study protocol (Lien et al., 2019). Only females were included. Peak VO_2 and VO_2 at the ventilatory threshold were significantly lower in ME/CFS patients vs. controls on day 1 and 2. Peak VO_2 and VO_2 at the ventilatory threshold decreased significantly at day 2 in patients but not in controls. Peak workload was significantly lower in ME/CFS patients and controls on day 1 and 2 and decreased significantly in both groups comparing day 2 with day 1. In

contrast workload at the ventilatory threshold was significantly lower in ME/CFS patients and controls on day 1 and 2 but decreased only significantly in ME/CFS patients on day 2.

Limitations:

We included no male sedentary controls for comparison in this study. This was not a prospective trial, as most patients underwent consecutive day CPET to provide evidence regarding the degree of disability for social security claims. Differences between the previously discussed studies and the present study might be in the demographic characteristics and illness severity of the study population, but also in the exact methodology of the CPET used in the different study centers. Reference values for predicted VO_2 can differ between studies as well.

5. Conclusion

This study in male ME/CFS patients shows that exercise capacity expressed in peak VO_2 , VO_2 at the ventilatory threshold and workload both at peak and at the ventilatory threshold decreased significantly on the second day of consecutive cardiopulmonary exercise testing. Previous reports included small numbers of male ME/CFS patients. Given the differences between males and females in factors such as muscle mass, hemoglobin, cardiac volumes, and lung volumes, it had been unclear whether males and females with ME/CFS would respond similarly on consecutive day CPET. The larger sample size of this study improves the confidence with which we can conclude that, like females, males have a similar decrement on day 2 of the consecutive day exercise tests. Our results confirm that 2-day CPET can be used in males to demonstrate the decrease in exercise capacity in research studies and if needed for social security claims. Further comparisons are needed to explore whether the absolute or relative changes in VO_2 and workload on day 2 versus day 1 are similar across a wider range of clinical severity, and whether these values differ for subgroups with specific comorbid conditions.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

- BMI: body mass index
CFS: chronic fatigue syndrome
CPET: cardiopulmonary exercise test
ME: myalgic encephalitis
VO₂: oxygen consumption
VO₂ VT: The VO₂ at the ventilatory threshold
VO₂ peak: The VO₂ at peak exercise