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Heart Rate Thresholds to Limit Activity in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Patients (Pacing): Comparison of Heart Rate Formulae and Measurements of the Heart Rate at the Lactic Acidosis Threshold during Cardiopulmonary Exercise Testing

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Abstract

Introduction: Based on the hypothesis that oxidative metabolism is impaired in ME/CFS, a previous study recommended a pacing self-management strategy to prevent post-exertional malaise. This strategy involved a prescription to maintain a heart rate below the anaerobic threshold during physical activities. In the absence of lactate sampling or a cardiopulmonary exercise test (CPET), the pacing self-management formula defines 55% of the age-specific predicted maximal heart rate as the heart rate at the anaerobic threshold. Thus far there has been no empiric evidence to test this self-pacing method of predicting heart rate at anaerobic threshold. The aim of this study was to compare published formula-derived heart rates at the anaerobic threshold with the actual heart rate at the lactic acidosis threshold as determined by CPET. **Methods and Results:** Adults with ME/CFS who had undergone a symptom-limited CPET were eligible for this study (30 males, 60 females). We analysed males and females separately because of sex-based differences in peak oxygen consumption. From a review paper, formulae to calculate maximal predicted heart rate were used for healthy subjects. We compared the actual heart rate at the lactic acid threshold during CPET to the predicted heart rates determined by formulae. Using Bland-Altman plots, calculated bias: the mean difference between the actual CPET heart rate at the anaerobic threshold and the formula predicted heart rate across several formulae varied between −28 and 19 bpm in male ME/CFS patients. Even in formulae with a clinically acceptable bias, the limits of agreement (mean bias ± 2SD) were unacceptably high for all formulae. For female ME/CFS patients, bias varied between 6 and 23 bpm, but the limits of agreement were also unacceptably high for all formulae. **Conclusion:** Formulae generated in an attempt to help those with ME/CFS exercise below the anaerobic threshold do not reliably predict actual heart rates at the lactic acidosis threshold as measured by a cardiopulmonary exercise test. Formulae based on age-dependent predicted peak heart rate multiplied by 55% have a wide age-specific variability and therefore have a limited application in clinical practice.

Keywords

Chronic Fatigue Syndrome, Myalgic Encephalomyelitis, Cardiopulmonary Exercise Testing, Peak Oxygen Consumption, Lactic Acidosis Threshold, Oxygen Consumption at the Anaerobic Threshold, Workload, Pacing, Heart Rate Formulae

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). One of the main characteristics of patients with ME/CFS is a prolonged recovery and an increase in symptoms following mental or physical exercise, termed post-exertional malaise (Jones et al., 2010; Paul et al., 1999). The duration of post-exertional malaise can vary between hours and months. The pathophysiology of post-exertional malaise is not exactly known but has been hypothesized to involve metabolic abnormalities, reduced efficiency of mitochondrial energy production, renin-angiotensin and sympathetic nervous system activation, central nervous system abnormalities, increased activity of antioxidant enzyme systems in muscle, alterations in the hypothalamic-pituitary-adrenal axis, altered immune responses, and an altered gut microbiomes with delayed clearance of blood bacteria following exercise (Bains, 2008; Blundell et al., 2015; Bohne & Bohne, 2019; Brown et al., 2015; Cordero et al., 1996; Fulle et al., 2000; Fulle et al., 2007; Ghali et al., 2019; Jones et al., 2010; Josev et al., 2019; Lien et al., 2019; Light et al., 2012; McCully et al., 2003; McGregor et al., 2019; Nguyen et al., 2017; Nijs et al., 2014; Shukla et al., 2015; Siemionow et al., 2004; Sorensen et al., 2009; Van Den et al., 2007; Whistler et al., 2005; Wong et al., 1992). Other studies have provided conflicting data for some of the hypothesized underlying mechanisms (Bouquet et al., 2019; Keech et al., 2016).

Based on the hypothesis that oxidative metabolism is impaired in ME/CFS, Davenport et al. recommended an exercise prescription that keeps the heart rate below the anaerobic threshold (Davenport et al., 2010) as a method for preventing post-exertional malaise. As there is a direct relation between the heart rate and the anaerobic threshold, the heart rate at the anaerobic threshold was advocated to be used as a guide for physical activities, aiming to avoid ineffective anaerobic metabolism in ME/CFS patients. This strategy has been referred to as pacing self-management.

The gold standard for measuring the anaerobic threshold is an exercise test with periodic lactate sampling. However, this method is laborious, expensive, invasive. In ME/CFS patients the exercise test itself can lead to post-exertional malaise. It has been previously demonstrated in sedentary controls that the lactate threshold (as a reflection of the anaerobic threshold) was 59 (8)% and 67 (7)% of the peak oxygen consumption in females and males, respectively (Demello et al., 1987), with heart rates at the anaerobic threshold being 69% of the peak heart rate in sedentary women and 77% of the peak heart rate in sedentary men. An alternative to determine the anaerobic threshold and the related heart rate is to use the lactic acidosis threshold as determined by the V-slope method during cardiopulmonary exercise testing (CPET) (Beaver et al., 1986). A previous study has shown that the heart rate at the lactic acidosis threshold is highly reproducible between tests (Aunola & Rusko, 1984).

For pacing purposes, without the use of lactate sampling or a CPET, formulae have been developed to approximate the heart rate at the anaerobic threshold. These formulae assume that the peak oxygen consumption is associated with the peak heart rate of an individual. The majority of these formulae are based on age (Robergs, 2002). These age-dependent peak heart rate calculations are in general used for training purposes of athletes. For ME/CFS patient-pacing purposes the heart at the anaerobic threshold is set at 55% of the peak heart rate. A popular formula to determine the heart rate at the anaerobic threshold is the calculation: 220-age * 55%. This formula has been adopted in patient websites for pacing self-management such as http://www.cfsselfhelp.org/library/pacing-numbers-using-your-heart-rate-to-stay-inside-energy-envelope and https://www.healthrising.org/?s=pacing.

However, no empiric data are available on the reliability of the proposed formula for determination of the heart rate at the anaerobic threshold in ME/CFS patients. Robergs and Landwehr performed a large review of the studies of age-dependent peak heart rate formulae in general, and found that there are large errors inherent in the estimation of the maximum heart rate (Robergs, 2002). Because it is based on these age-dependent peak heart rate formulae, the proposed pacing self-management formula for ME/CFS patients, is susceptible to similar methodologic errors. Therefore, the aim of this study was to compare the proposed formula-derived heart rate at the anaerobic threshold with the actual heart rate at the lactic acidosis threshold as determined by CPET.

2. Patients, Material and Methods

Eligible participants were male and female ME/CFS patients referred between 2012 and 2018 to the Stichting CardioZorg. This cardiology clinic specializes in diagnosing and treating adults with ME/CFS. The diagnosis of chronic fatigue syndrome (CFS) was made according to the Fukuda criteria (Fukuda et al., 1994) and that of myalgic encephalomyelitis (ME) was made according to the international ME criteria (Carruthers et al., 2011). In all patients alternative diagnoses which could explain the fatigue and other symptoms were ruled out. No important co-morbidities were present.

This study included the subset of patients in whom CPET was performed. The decision to perform CPET was made primarily to assess the degree of disability. Because of the female predominance in ME/CFS, we choose a 2:1 female/male ratio. Females and males were age-matched, due to the dependence of the age of subjects in the heart rate formulae. Patients were excluded when the lactic acidosis threshold of the CPET could not be accurately assessed. Males and females were analysed separately because of sex-specific differences in peak oxygen consumption, and because of possible sex-specific differences in the clinical phenotype of the disease (Faro et al., 2016).

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.

***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 (van Campen et al., 2020). 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, Procare, 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. 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 lactic acidosis threshold (LAT) is an analog of anaerobic threshold, and was identified from expired gases using the V-Slope algorithm in the metabolic measurement system software. A trained investigator performed visual assessment and confirmation of the algorithm-derived LAT. Testing took place in a controlled environment with temperature range of 20˚C - 24˚C and 15% - 60% relative humidity. The test was supervised by an experienced cardiologist. 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, and expressed as a percentage of the normal values of a population study: %peak VO_2 (Glaser et al., 2010). We assessed the mean respiratory exchange ratio (RER; VCO_2/VO_2) of the last 15 seconds to determine the influence of this measure of maximal effort on the results. Immediately after the test the attending cardiologist noted the primary reason for terminating the exercise and judged whether motivation and efforts during exercise were optimal for the individual patient.

Formulae to calculate maximal predicted heart rate

From a review of published formulae to calculate maximal predicted heart rate, we selected those formulae used for healthy subjects. Formulae used in populations with diseases like hypertension, coronary heart disease, obesity, and mental retardation were excluded (Robergs, 2002). To obtain the predicted heart rate at the lactic acidosis threshold using the pacing self-management formula of Davenport et al., the predicted maximal heart rate from each individual formula was multiplied by 0.55 (Davenport et al., 2010). The patient data were used for all formulae to calculate maximal and anaerobic threshold. Those data were compared with the data resulting from the cardiopulmonary exercise test.

Table 1. Formulae for predicting maximal heart rate.

Men			Women		
Author	**Year**	**Formula**	**Author**	**Year**	**Formula**
Astrand (in Froelicher) (Froelicher & Jonathan, 2000)	2000	211-0.922*age	Brick (in Froelicher) (Froelicher & Jonathan, 2000)	2000	226-age
Bruce (Bruce et al., 1974)	1974	210-0.662*age	Fernhall (Fernhall et al., 2001)	2001	205-0.64*age
Cooper (in Froelicher) (Froelicher & Jonathan, 2000)	2000	217-0.845*age	Fox (Fox et al., 1971)	1971	220-age
Ellestad (in Froelicher) (Froelicher & Jonathan, 2000)	2000	197-0.556*age	Hossack (Hossack & Bruce, 1982)	1982	206-0.597*age
Fernhall (Fernhall et al., 2001)	2001	205-0.64*age	Inbar (Inbar et al., 1994)	1994	205.8-0.685*age
Fox (Fox et al., 1971)	1971	220-age	Jones (cycle) (Jones et al., 1985)#	1985	202-0.72*age
Froelicher (in Froelicher) (Froelicher & Jonathan, 2000)	2000	207-0.64*age	Jones (Jones et al., 1985)#	1985	201-0.63*age
Graettinger (Graettinger et al., 1995)	1995	199-0.63*age	Lester (untrained) (Lester et al., 1968)	1968	198-0.41*age
Hossack (Hossack & Bruce, 1982)	1982	227-1.067*age	Ricard (treadmill) (Ricard et al., 1990)	1990	209-0.687*age
Inbar (Inbar et al., 1994)	1994	205.8-0.685*age	Schiller (Caucasian) (Schiller et al., 2001)	2001	207-0.62*age
Jones (Jones et al., 1985)	1985	202-0.72*age	Sheffield (Sheffield et al., 1978)	1978	216-0.88*age
Lester (untrained) (Lester et al., 1968)	1968	198-0.41*age	Tanaka (sedentary) (Tanaka et al., 2001)*	2001	211-0.8*age
Morris (in Froelicher) (Froelicher & Jonathan, 2000)	2000	196-0.72*age	Tanaka (Tanaka et al., 2001)*	2001	208-0.7*age
Ricard (treadmill) (Ricard et al., 1990)	1990	209-0.687*age	Website cfsselfhelp	2018	206-0.88*age
Robinson (in Froelicher) (Froelicher & Jonathan, 2000)	2000	212-0.775*age	Whaley (Whaley et al., 1992)	1992	209-0.7*age
Rodeheffer (Rodeheffer et al., 1984)	1984	214-1.02*age			
Tanaka (sedentary) (Tanaka et al., 2001)*	2001	211-0.8*age			
Tanaka (Tanaka et al., 2001)*	2001	208-0.7*age			
Whaley (Whaley et al., 1992)	1992	214-0.8*age			

* and #: two different formulae for males and females described in the same paper.

Statistical analysis

Data were analyzed using Graphpad 6.05. All continuous data were tested for normal distribution using the D'Agostino-Pearson omnibus normality test, and data are presented as the mean (SD) or as median (IQR), where appropriate. Bland-Altman plots were generated comparing the heart rate at the lactic acidosis threshold and the formula-generated heart rates at the anaerobic threshold. Bias and limits of agreement were calculated. The bias is computed as the mean value of the subtraction: the heart rate at the lactate acidosis threshold minus the formula-derived heart rate at the anaerobic threshold of all patients. Limits of agreement are calculated as the mean bias plus or minus two standard deviations. A clinically acceptable bias was predefined and set at plus or minus 5 bpm. Furthermore, linear regression analysis was performed on the mean heart rates of both methods vs the differences of both methods, to assess the presence of proportional bias. The proportional bias means that one method gives values that are higher (or lower) than those from the other by an amount that is proportional to the level of the measured variable (Ludbrook, 1997). Differences in variance were assessed using the F test. A P value < 0.01 was considered significantly different.

3. Results

Table 2 shows the characteristics of the study participants (30 male ME/CFS patients and 60 female ME/CFS patients). Males were significantly taller and heavier than females. Disease duration did not differ significantly. Resting heart rate was significantly higher for women and peak systolic blood pressure significantly higher in men. Workload and VO_2 at the lactic acidosis threshold and at peak exercise were significantly higher in men than in women. In contrast, % predicted VO_2 at the lactic acidosis threshold and peak were not significantly different between men and women.

Figure 1 shows an example of the formula predicted heart rate at the anaerobic threshold vs the heart rate of the lactic acidosis threshold by CPET in patients. Figure 1(a) shows the heart rate at the anaerobic threshold using the prediction formula: 220-age (Fox et al., 1971) * the multiplier 0.55 (Davenport et al., 2010) for the 30 male ME/CFS patients compared with the actual heart rate at the lactic acidosis threshold of CPET. Figure 1(b) shows the anaerobic threshold heart rate data of the same prediction formula: (220-age) × 0.55 for the 60 female ME/CFS patients versus the heart rate at the lactic acidosis threshold. Both in males and females variance of the heart rate at the lactic acidosis threshold was larger than that of the formula (both $p < 0.01$)

Table 3(a) shows the results of the Bland-Altman analysis of the different heart rate prediction formulae of Table 1 versus the heart rate at the lactic acidosis threshold for male ME/CFS patients. Bias varied between −28 and 19 bpm, but even in formulae with a clinically acceptable bias, the limits of agreement are unacceptably high for all formulae (arbitrarily set at a bias of plus/minus 5 bpm).

Table 3(b) shows the same analysis for female ME/CFS patients. Bias varied between 6 and 23 bpm, but also in women the limits of agreement were also unacceptably high for all formulae. An example of the Bland-Altman analysis (formula based on the maximal predicted heart rate of Lester et al. (Lester et al., 1968) for men and women is shown in Figure 2(a) and Figure 2(b). Furthermore, a proportional bias analysis was performed (Ludbrook, 1997). Table 3(a) and Table 3(b) show that all the regression lines of the mean of the prediction heart rate and the heart rate at the lactic acidosis threshold vs the differences between the two heart rates were highly significantly different from zero, indicating proportional bias. An example of this proportional bias is given in Figure 2(c) and Figure 2(d).

To further explore the differences between the predicted heart rate at the anaerobic threshold and the actual heart rate at the lactic acidosis threshold during CPET we plotted patient age versus the heart rate at the lactic acidosis threshold. This was done because age determines the calculated heart rate at the

Table 2. Baseline and cardiopulmonary exercise test data for male and female CFS patients.

	M ME/CFS (n = 30)	F ME/CFS (n = 60)	*P* value
Age (years)	41 (13)	42 (9)	0.8611
Height (cm)	181 (8)	170 (7)	<0.0001
Weight (kg)	81 (15)	71 (14)	<0.0001
BSA duBois (m^2)	1.7 (0.2)	1.4 (0.2)	<0.0001
BMI (kg/m^2)	26.6 (4.5)	24.7 (4.6)	0.0715
Disease duration (years)	10 (7-13)	12 (9-20)	0.1873
Heart rate rest (bpm)	79 (12)	88 (11)	0.0017
Heart rate LAT (bpm)	110 (14)	116 (13)	0.0302
Heart rate peak (bpm)	149 (23)	151 (19)	0.7049
Systolic BP rest (mmHg)	126 (17)	123 (13)	0.3251
Systolic BP peak (mmHg)	188 (25)	162 (18)	<0.0001
Diastolic BP rest (mmHg)	81 (9)	82 (9)	0.8222
Diastolic BP peak (mmHg)	107 (12)	99 (12)	0.0104
Workload LAT (watt)	100 (32)	60 (19)	<0.0001
Workload peak (watt)	199 (55)	121 (30)	<0.0001
VO_2 at LAT (ml/min/kg)	15 (5)	12 (2)	<0.0001
VO_2 peak (ml/min/kg)	26 (8)	19 (5)	<0.0001
Perc predicted VO_2 at LAT (%)	42 (14)	44 (10)	0.4599
Perc predicted VO_2 at peak (%)	72 (21)	69 (17)	0.4594
RER	1.1 (0.12)	1.1 (0.11)	0.1330

BMI: body mass index; no: number; BP: blood pressure; BSA: body surface area; F: female; M: male; Perc: percent; RER: respiratory exchange ratio; VO_2: oxygen consumption; LAT: lactic acidosis threshold. Data are expressed as mean (SD) or median (25% - 75% IQR).

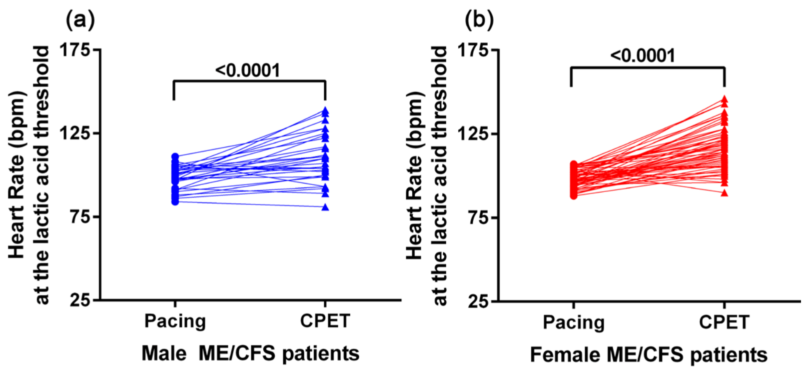


Figure 1. An example of the formula of the predicted heart rate at the anaerobic threshold vs the heart rate at the lactic acidosis threshold by CPET in ME/CFS patients. (a) shows the data in men using the prediction formula: (220-age) × 0.55 using the Fox et al. 1971 formula and the 0.55 multiplier from Davenport. (b) shows the data in females using the same prediction formula: (220-age) × 0.55. Both in males and females variance of the heart rate at the lactic acidosis threshold was larger than that of the formula (both $P < 0.01$). CPET: cardiopulmonary exercise test; AT: anaerobic threshold; LAT: lactic acidosis threshold.

Table 3. (a) Heart rates at the lactic acidosis threshold using different peak heart rate formula, bias and limits of agreement of formula vs the heart rate at the lactic acidosis threshold (Bland-Altman plots) in men; (b) Heart rates at the lactic acidosis threshold using different peak heart rate formula, bias and limits of agreement of formula vs the heart rate at the lactic acidosis threshold (Bland-Altman plots) in women.

(a)

Male ME/CFS patients (n = 30) with HR LAT 110 (14) bpm				
Author	Mean HR AT calc (bpm)	Bias HR LAT − HR calc I (bpm)	Limits of agreement (bpm)	Proportional bias analysis significant*
Astrand (Froelicher & Jonathan, 2000)	138 (7)	-28	−64 to 8	<0.0001
Bruce (Bruce et al., 1974)	100 (5)	9	−17 to 35	<0.0001
Cooper (Froelicher & Jonathan, 2000)	100 (6)	10	−16 to 36	<0.0001
Ellestad (Froelicher & Jonathan, 2000)	96 (4)	14	−12 to 40	<0.0001
Fernhall (Fernhall et al., 2001)	98 (4)	6	−8 to 20	<0.0001
Fox (Fox et al., 1971)	98 (7)	12	−14 to 38	<0.001
Froelicher (Froelicher & Jonathan, 2000)	99 (4)	11	−15 to 37	<0.0001
Graettinger (Graettinger et al., 1995)	95 (4)	15	−11 to 41	<0.0001
Hossack (Hossack & Bruce, 1982)	101 (7)	9	−17 to 35	0.0002
Inbar (Inbar et al., 1994)	98 (5)	12	−14 to 38	<0.0001
Jones (cycle) (Jones et al., 1985)	95 (5)	6	−20 to 32	<0.0001
Lester (Lester et al., 1968)	100 (3)	10	−16 to 36	<0.0001
Morris (Froelicher & Jonathan, 2000)	91 (5)	19	−7 to 45	<0.0001
Ricard (Ricard et al., 1990)	99 (5)	11	−15 to 37	<0.0001
Robinson (Froelicher & Jonathan, 2000)	99 (5)	11	−15 to 37	<0.0001
Rodeheffer (Rodeheffer et al., 1984)	95 (7)	15	−11 to 41	<0.001
Tanaka (sedentary) (Tanaka et al., 2001)*	98 (5)	12	−14 to 38	<0.0001
Tanaka (Tanaka et al., 2001)*	98 (5)	11	−15 to 37	<0.0001
Whaley (Whaley et al., 1992)	100 (5)	10	−16 to 36	<0.0001

*: two different formulae for males and females described in the same paper. AT: anaerobic threshold; bpm: beats per minute; calc: calculated; HR: heart rate; LAT: lactic acidosis threshold; *proportional bias analysis significant: significance of the linear regression analysis of the mean heart rate of the two methods versus the difference between the two methods.

(b)

Female ME/CFS patients (n = 60) HR LAT 116 (13) bpm				
Author	Mean HR AT calc (bpm)	Bias HR LAT − HR calc I (bpm)	Limits of agreement (bpm)	Proportional bias analysis significant*
Brick (Froelicher & Jonathan, 2000)	101 (5)	6	−22 to 34	<0.0001
Fernhall (Fernhall et al., 2001)	98 (3)	15	−9 to 39	<0.0001
Fox (Fox et al., 1971)	98 (5)	18	−6 to 42	<0.0001
Hossack (Hossack & Bruce, 1982)	100 (3)	17	−7 to 41	<0.0001
Inbar (Inbar et al., 1994)	97 (4)	10	−2 to 22	<0.0001
Jones (cycle) (Jones et al., 1985)#	95 (4)	22	−2 to 46	<0.0001
Jones (Jones et al., 1985)#	96 (3)	20	−4 to 44	<0.0001
Lester (Lester et al., 1968)	99 (2)	17	−7 to 41	<0.0001
Ricard (Ricard et al., 1990)	99 (4)	17	−7 to 41	<0.0001
Schiller (Schiller et al., 2001)	100 (3)	17	−7 to 41	<0.0001
Sheffield (Sheffield et al., 1978)	99 (5)	18	−6 to 42	<0.0001
Tanaka (sedentary) (Tanaka et al., 2001)*	98 (4)	19	−5 to 43	<0.0001
Tanaka (Tanaka et al., 2001)*	98 (4)	18	−6 to 42	<0.0001
Website CFSselfhelp (see methods)	93 (5)	23	−1 to 47	<0.0001
Whaley (Whaley et al., 1992)	99 (4)	18	−6 to 42	<0.0001

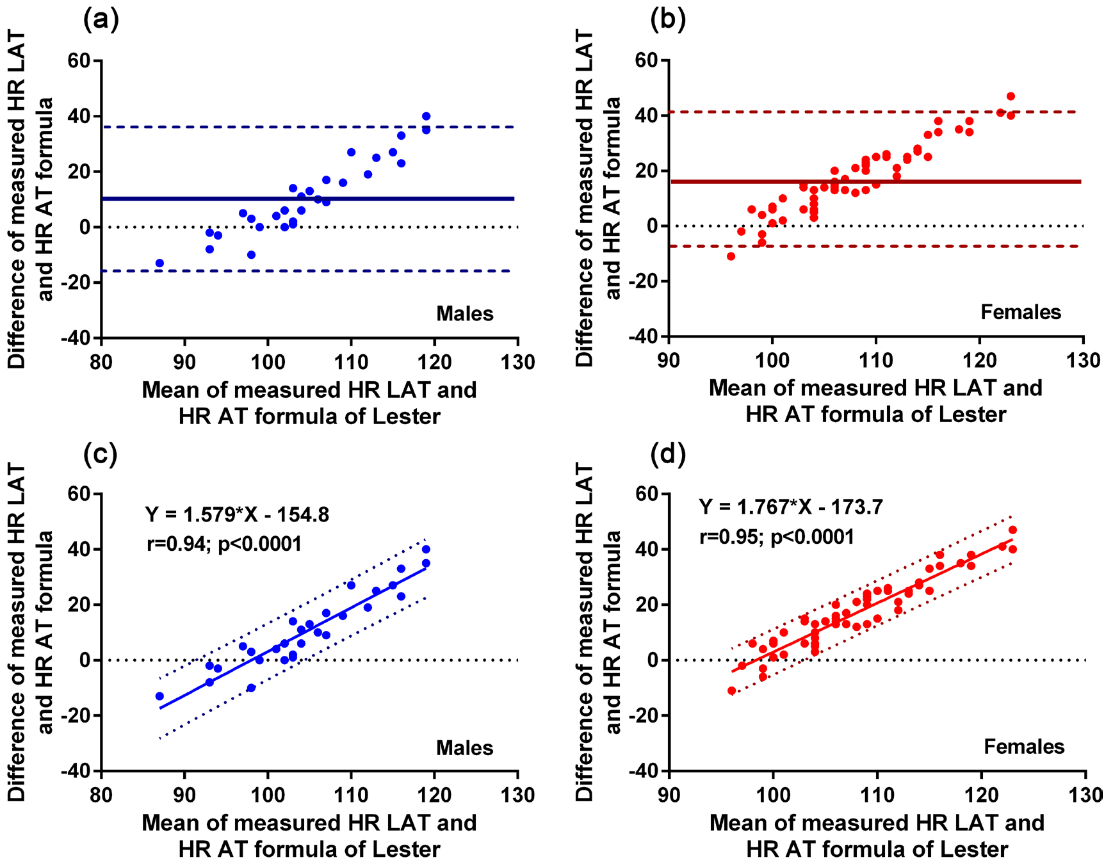
* and #: two different formulae for males and females described in the same paper. For other abbreviations see Table 3(a).

anaerobic threshold. Figure 3 shows that age has a limited influence on the heart rate at the lactic acidosis threshold. The slopes of the regression line were non-significantly different from zero both in men and women and slopes were not significantly different between men and women. The actual heart rate at the lactic acidosis threshold for female ME/CFS patients ranged from 90 to 146 bpm and for male ME/CFS patients from 81 to 139 bpm.

4. Discussion

One of the main findings of this study was that the heart rate at the lactic acidosis threshold is minimally influenced by the age of the ME/CFS patients, whereas, by definition, the calculated heart rate at the anaerobic threshold is highly dependent on age. Thus, not only the formula 220-age, but also the other explored formulae in the present study are only of limited use for pacing strategies in ME/CFS patients.

One of the hallmarks of ME/CFS is a reduced capacity for physical and mental exercise (Carruthers et al., 2003; IOM, 2015; Peterson et al., 1994), ranging from mild to very severe. The most severely affected ME/CFS patients are bedridden and need assistance from others for activities of daily living (De Becker et al., 2000; Vanness et al., 2003). Post-exertional malaise with flare-up of symptoms after a mental or physical exercise, which exceeds the limited performance capacity of ME/CFS patients, is another serious problem for ME/CFS patients



CPET: cardiopulmonary exercise test; AT: anaerobic threshold; LAT: lactic acidosis threshold. In each panel, the distance between zero and the thick solid line is the bias of the formula-based HR measurement. The dashed lines represent 2SD from that mean. In an ideal test, the bias would be close to zero. For Panels (c) and (d), an ideal test would have a non-significant slope.

Figure 2. Shows the comparison of the heart rate at the lactic acidosis threshold measured at CPET (method (a)) and the heart rate at the anaerobic threshold using the formula by Lester (method (b)) (Lester et al., 1968). Panels (a) and (b) show Bland-Altman plots for male (panel (a)) and female (panel (b)) ME/CFS patients. Panels (c) and (d) show the proportional bias regression analysis for male (panel (c)) and female (panel (d)) ME/CFS patients.

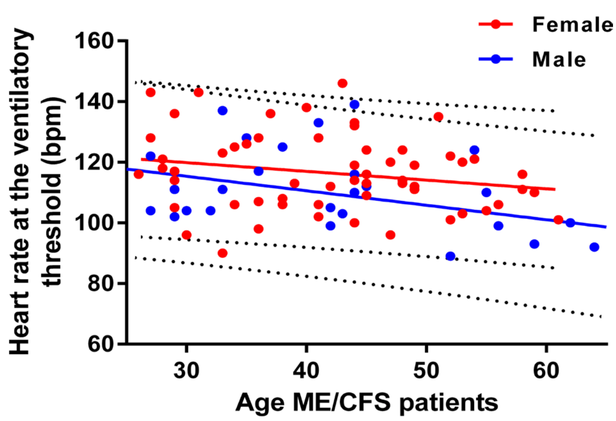


Figure 3. Correlation of heart rate at the lactic acidosis threshold as measured during CPET and age in both males (blue dots) and females (red dots) ME/CFS patients. The slopes of the regression line of age versus the heart rate at the lactic acidosis threshold were not significantly different from zero and slopes between men and women were not significantly different. The dotted lines are 95% prediction intervals.

because the increase in symptoms further limits daily activities (Davenport et al., 2011; Vanness et al., 2010). The importance of post-exertional malaise is exemplified in the diagnostic criteria of ME, as without the presence of post exertional malaise, the diagnosis ME cannot be made (Carruthers et al., 2011).

To reduce post-exertional malaise in ME/CFS patients strategies, called "pacing" have been developed. Nijs et al. (Nijs et al., 2008) suggested pacing to encourage patients to balance activities and rest to ensure no deterioration of symptoms. This strategy should include realistic goals and monitoring of exercise and effects on energy balance. Also, fluctuations in symptom severity and delayed recovery from exercise due to post-exertional malaise should be taken into account. Activities should be varied with pauses in duration related to the duration of performed activities.

Based on the observation that oxidative metabolism may be impaired in ME/CFS, Davenport et al. recommended, to avoid post-exertional malaise, exercise prescription below the anaerobic threshold (Davenport et al., 2010). As there is a direct relation between the heart rate and the anaerobic threshold (Aunola & Rusko, 1984), the heart rate at the anaerobic threshold was advocated to be used as a guide for physical activities, aiming to avoid ineffective anaerobic metabolism in ME/CFS patients. Although intuitively the use of this heart rate at the anaerobic threshold as an upper limit of performed activity may be correct, there are no studies available demonstrating the effectiveness of this approach. Indirect evidence may come from graded exercise therapy studies. Assuming that during graded exercise therapy the training involves frequent activities above the anaerobic threshold, patients reported deterioration in physical functioning (Davenport et al., 2010) after graded exercise therapy. Also, a study of Black et al. showed an increase in activity of ME/CFS patients with exercise therapy early in the study, but a large decline in activity duration at the end of the trial (Black & McCully, 2005).

There are shortcomings in using the formula 220-age for the prediction of the maximum heart rate. Roberg et al. stated: "Despite the acceptance of this formula, research spanning more than two decades reveals the large error inherent in the estimation of HRmax". Furthermore: "A brief review of alternate HRmax prediction formula reveals that the majority of age-based univariate prediction equations also have large prediction errors" (Robergs, 2002). The second statement suggests that there may be accurate formula to predict age dependent peak heart rates. Furthermore, the choice of assigning the heart rate at the anaerobic threshold at 55% of the peak heart rate has also not been validated in the ME/CFS population.

Therefore, the aim of this study was to compare predicted heart rates at the anaerobic threshold, using different published peak heart rate formula and applying the Davenport et al. 55% multiplier for ME/CFS patients, with the actual heart rate at the lactic acidosis threshold as determined by cardiopulmonary exercise stress testing. The main finding of this study was that all formulae used to calculate predicted heart rate at the anaerobic threshold showed a large variation in bias, but more importantly, a clinically unacceptable range in the limits of agreement. The large range in limits of agreement was due to the presence of proportional bias, meaning that one method gives values that are higher (or lower) than those from the other by an amount that is proportional to the level of the measured variable (Ludbrook, 1997). The difference between formulae and the measurement of the heart rate at the lactic acidosis threshold is shown in **Figure 3**. The heart rate at the lactic acidosis threshold is minimally influenced by the age of the ME/CFS patients, whereas, by definition, the calculated heart rate at the anaerobic threshold is highly dependent on age. Thus, not only the formula 220-age, but also the other explored formulas in the present study are not clinically useful for pacing strategies in ME/CFS patients. The usefulness of the formula in other diseases than ME/CFS need to be studied in future, as some might be potentially detrimental if followed rigidly.

Potential limitations have to be mentioned. This was a retrospective study that selected patients who had undergone cardiopulmonary exercise stress testing, mainly to establish the degree of disability for social security claims. This may have led to inclusion bias. On the other hand, baseline characteristics of the present study like age (Keller et al., 2014; Snell et al., 2013), workload (Keller et al., 2014; Nelson et al., 2019) and oxygen consumption at the lactic acidosis threshold (Van Campen, 2020; Vermeulen & Vermeulen van Eck, 2014) and at peak exercise (Keller et al., 2014; Van Campen, 2020) (**Table 1**), are consistent with other studies. Second, the heart rate at the lactic acidosis threshold, as determined during the cardiopulmonary exercise test, has been used as the standard for the heart rate at the anaerobic threshold. The exact point where CO_2 output starts to rise disproportionally, relative to the oxygen consumption, may be difficult to assess because of irregular breathing, suboptimal plotting or a poor ventilatory response (Wasserman et al., 2012). In that case the value of the oxygen consumption and related heart rate at that point may be different from the true values. Although a trained investigator performed visual assessment and confirmation of the algorithm-derived lactic acidosis threshold, we cannot exclude the possibility of erroneous heart rate values.

5. Conclusion

Calculated heart rates at the anaerobic threshold, based on age-dependent peak heart formula times a fixed percentage of 55%, with the aim to limit ME/CFS patients to perform exercise below the anaerobic threshold, do not reliably predict heart rates at the lactic acidosis threshold as measured by a cardiopulmonary exercise test and should be used with caution in clinical practice.

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Conflicts of Interest

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

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