A study investigating the role of the resting Respiratory Exchange Ratio (RER) in patients with Myalgic Encephalomyelitis and Chronic Fatigue Syndrome.

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Background of Author:

I have recently finished my Postgraduate Master's in Clinical Research at Norwich Medical School, part of the University of East Anglia. At the age of 15 I was diagnosed with ME/CFS, upon experiencing that there was no standard treatment I decided I would try and look into it, as I had a keen interest in science. 10 years later I was able to complete this study in ME/CFS as my Master Thesis.

Introduction:

What is ME?

Myaglic Encephalomyelitis (ME) and Chronic Fatigue Syndrome (CFS) are often used interchangeably, although some literature argues they are different conditions. ME is characterised by pain, fatigue and neurocognitive dysfunction (Paul *et al.,* 1999), and is thought to involve the distortion of homeostasis (natural bodily balance) across multiple organ systems. These systems are thought to be the Central Nervous System, Immune System, Energy Metabolism Systems and the Cardiovascular System (Carruthers *et al.,* 2011). The National Institute of Health Care and Excellence (NICE) estimate between 0.2% and 0.4% of the population of the UK suffer with ME (NICE, 2007), this equates to 250,000 people or 1 in every 250 people.

What is CFS?

CFS was introduced to describe an unexplained illness by the Centre of Disease Control and Prevention (CDC) in the 1980's, after research failed to obtain a link between the unexplained illness and the Epstein-Barr Virus (also called Glandular Fever). CFS is a disease of chronic and often disabling fatigue often accompanied by other associated symptoms. It is not known to be caused by any obvious medical or psychological disease (Reeves *et al.,* 2005: Prins, van der Meer and Bleijenberg*,* 2006). Studies have shown between 0.007% and 2.5% of the population of the UK suffer from CFS, meaning there are between 5000 and 170,000 cases of CFS (Jason *et al.,* 1999).

What is the RER?

The Respiratory Exchange Ratio (RER) is a physiological measure used to determine physical effort. It is a ratio between the amount of carbon dioxide the body produces and the amount of oxygen the body consumes (CO_2/O_2). It indirectly shows the body's capability to acquire energy. A high RER indicates a higher Oxygen usage, meaning more energy expenditure. Typically, RER measurements are taken at peak exercise, however, this study uses it at rest, where a healthy person's resting RER is no greater than 0.8. This study is designed to find if people with ME/CFS have a higher resting RER. This has to be done under fasting conditions because RER can also be used to calculate the energy gain from certain food groups (Simonson and DeFronzo, 1990; Pendergast *et al.* 2000).

A higher RER also suggests a person might have either an increased concentration of carbon dioxide or a reduced concentration of oxygen, both of these inhibit energy production.

Hypothesis:

1. The Respiratory Exchange Ratio is significantly elevated in Myalgic Encephalomyelitis patients compared to the known historical healthy controls (HHC).
2. The Respiratory Exchange Ratio is significantly elevated in Chronic Fatigue Syndrome patients compared to the known HHC.
3. The Respiratory Exchange Ratio is significantly different between Myalgic Encephalomyelitis and Chronic Fatigue Syndrome.
4. There will be a positive relationship between the severity of symptoms and Respiratory Exchange Ratio.

Methodology:

Who Were the Participants?

The study sample included 2 groups of subjects, those with a diagnosis of CFS using the Fukuda Criteria for Chronic Fatigue Syndrome (Fukuda *et al.,* 1994; Reeves *et al.,* 2003) and those with a diagnosis of ME using the International Consensus Criteria for Myalgic Encephalomyelitis (Carruthers *et al.,* 2011).

Sixteen participants were recruited from the East Coast Community Healthcare which is a community interest company, that take referrals from the National Health Service (NHS) in Norfolk and Suffolk.

No one under the age of 18, or people who could not give informed consent were enrolled into the study.

The study took place at the University of East Anglia, upon entry participants signed a consent form, and completed baseline assessments which was carried out through a questionnaire booklet. The questionnaire booklet was comprised of 5 questionnaires: Chalder Fatigue Scale (Chalder *et al.* 1993), SF-36 Physical Functioning Sub-Scale (Ware and Sherbourne, 1992), International Pain Assessment Tool (Breivik *et al.,* 2008), Jenkins Sleep Scale (Jenkins *et al.* 1988) and the Borg Perceived Effort Scale (Borg, 1970). This allowed a quick assessment of the participants condition. The participants completed both the ME and CFS diagnostic criteria which allowed the participant to be sorted into their relevant group, ME or CFS.

The Protocol:

Specialist computer software and equipment was used to calculate different cardiovascular measures, including the RER. Participants wore heart rate monitors and a face mask with a sensor built in which was connected to the computer. This lasted 20 minutes which was done while laying on a bed to ensure a resting RER. The main data produced were oxygen consumption, carbon dioxide production, RER, Respiratory Rate (how many breaths a minute) and heart rate.

Tea, coffee and biscuits were provided as participants had not eaten or drank in 12 hours.

Ethical Approval:

The study protocol was approved by the South-Central Berkshire Research Ethics Committee. As this was a student study there was no financial incentive.

What analysis was done?

Analysis was completed using computer software, allowing both the data and the participants characteristics to be compared. The RER was compared to each group, ME/CFS, CFS and HHC using an ANOVA (type of statistical test). Univariate and multivariate linear regression (another statistical test, used to determine relationships between the independent variable, RER and the dependant variables, i.e., BMI or age) was used to associate characteristics back to the RER. Statistical significance was accepted if the P value was less than 0.05 (a standard figure in statistics).

Results:

Participant Data:

Of the 16 participants enrolled 15 tested positive to CFS according to the Fukuda Criteria. While 6 tested positive for ME according to the International Consensus Criteria. Only one tested positive for ME and not CFS. As a result of this we decided to name to two groups CFS and ME/CFS as it best described the outcome.

Age, gender and duration of illness were not significantly different between the 2 diagnosis groups, however BMI had a higher value in the ME/CFS group compared to the CFS group, as shown in Table 1.

Table 1: Demographical Data of the Participants (± SD unless otherwise stated)

	CFS (n = 10)	ME/CFS (n = 6)	P-Value
Age (Years)	54.6 (15.4)	38.0 (14.8)	0.053
Gender (Female) (%)	8 (80%)	5 (83.3%)	0.879
BMI (Kg/m^2)	25.85 (4.21)	34.67 (6.21)	0.040 *
Duration of illness (Months)	119.4 (81.41)	128.00 (128.28)	0.871

CFS= Chronic Fatigue Syndrome; ME = Myalgic Encephalomyelitis; * = P=<0.05; ** = P= < 0.01; *** = P= <0.001.

Participants data from the questionnaires, shown in Table 2, indicate there were no significant differences between the questionnaire scores and diagnosis.

Table 2: Questionnaire scores [mean ± Standard Deviation]

	CFS (n=10)	ME/CFS (n=6)	P-Value
Chalder Fatigue Score	26.50 (4.97)	25.33 (5.39)	0.607
SF-36 Sub-scale	9.20 (6.14)	9.67 (6.71)	1.000
Jenkins Sleep	11.30 (4.40)	13.33 (2.94)	0.302
International Pain Score	2.65 (1.89)	4.50 (2.07)	0.299
Borg Effort Score	12.40 (5.02)	11.83 (2.99)	1.000

CFS= Chronic Fatigue Syndrome; ME = Myalgic Encephalomyelitis; * = P=<0.05; ** = P= < 0.01; *** = P= <0.001.

Where did the Control Data come from?

The data for the healthy controls came from historical studies, where healthy participants had their RER measured at rest, 4 studies were used to calculate an average with standard deviations and standard errors.

Data Analysis:

Analysis showed the mean RER of ME/CFS participants was significantly (shown by the p-value being less than 0.05) elevated compared to the HHC, as shown in Table 3. Similarly, the RER in CFS participants was significantly elevated compared to the HHC. However, the RER was not significantly different between the ME/CFS group and the CFS group.

Table 3: RER analysis by ANOVA and Tukey post-hoc testing

	Mean	*Standard Deviation:*	*Compared with:*	*Significance (P – Value < 0.05)(When P is less than 0.05 the results are significantly different)*
CFS (n =10)	*0.966*	*0.091*	ME/CFS	*0.698*
			Control	*0.006***
	0.998	*0.066*	CFS	*0.698*

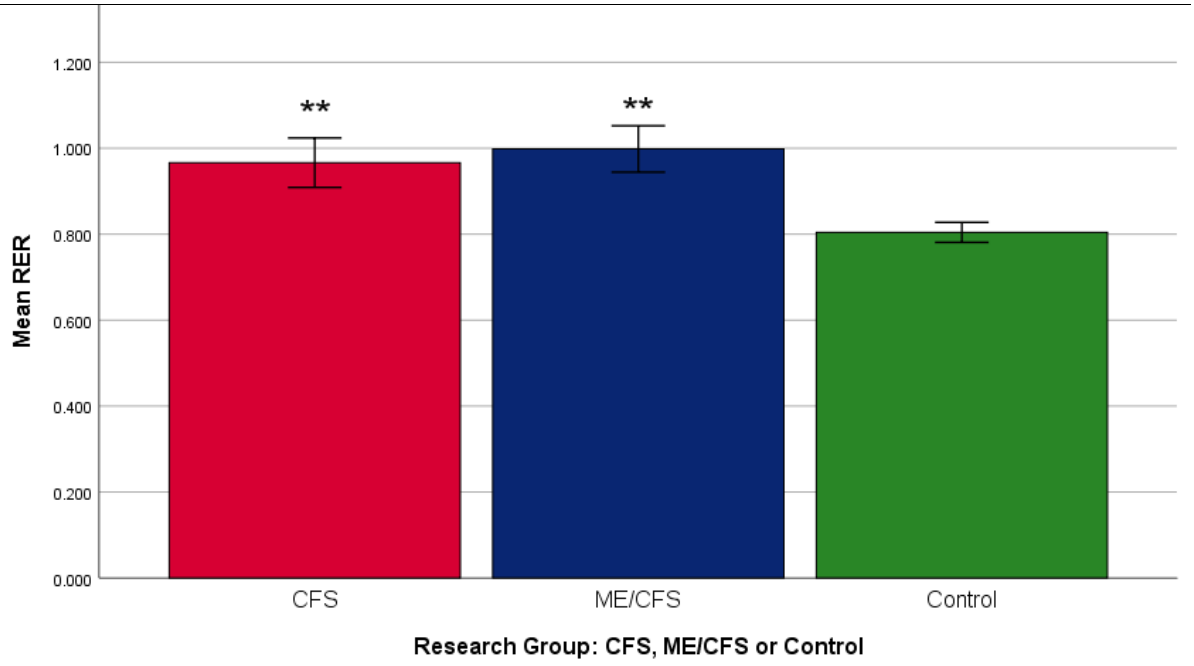
ME/CFS (n = 6)			Control	*0.003***
Control (n = 4)	*0.804*	*0.023*	CFS	*0.006***
			ME/CFS	*0.003***

CFS= Chronic Fatigue Syndrome; ME = Myalgic Encephalomyelitis; * = P=<0.05; ** = P= < 0.01; *** = P= <0.001.

This means hypotheses 1 and 2 cannot be rejected (hypotheses are never accepted, as nothing is 100% known), while hypothesis 3 can be rejected.

Figure 1 shows the data graphically allowing more obvious assumptions to be made, if the error bars overlap there is no significant difference between the groups.

Figure 1: Respiratory Exchange Ratio values across the research groups, when compared to the Control



CFS = Chronic Fatiuge Syndrome; ME = Myalgic Encephalomyelitis; Error bars show ± 2 Standard Error; * = P=<0.05; ** = P= < 0.01; *** = P= <0.001 (when compared with the control)

Linear regression models showed no relationship between the questionnaire scores (severity of illness) and mean RER. Therefore, hypothesis 4 was not accepted.

Discussion:

This study highlighted certain physiological symptoms and respiratory values. There is no study that has examined the RER at rest in ME and CFS patients. The reasoning behind the study was a theory that a person with either ME or CFS would have a higher RER than a healthy comparison. This is because they are thought to have a reduced energy and potentially mitochondrial (energy producing part of the cells) deficiencies and defects (Vecchiet *et al.,* 1996).

As the two researchers were not clinicians and 15 of the 16 participants had CFS according to the Fukuda Criteria, and 5 of the 15 also had the correct symptoms for ME, according to the International Consensus Criteria, therefore the terms ME/CFS was used. 1 participant only tested positive using the International Consensus Criteria while testing negative to the Fukuda Criteria.

Significant evidence was found to support the hypothesis that RER values were elevated in both CFS and ME/CFS participants in this study when compared to HHC. However, the research did not show a significant difference in RER values between ME/CFS and CFS diagnoses. The research did not show there to be a significant relationship between the symptoms and characteristics of either ME or CFS and in difference in RER, meaning a participant with more severe symptoms did not have an elevated RER compared to a participant with less severe symptoms.

A higher RER at rest indicates more oxygen is being used in everyday activities, this is because carbon dioxide is barely absorbed into the bloodstream. As RER is calculated as carbon dioxide divided by oxygen it is therefore a smaller concentration of oxygen will increase the RER (Vanhees et al. 2005).

Based on this data it can be proposed that people with ME and CFS have a higher RER indicating that their body is not working as efficiently as the HHC. This is because a higher RER indicates more cellular respiration, and more ATP (energy) production. While it is unclear why there is more oxygen consumption, what is clear is that their body is working harder to perform simple tasks.

Limitations:

The main limitation was sample size, as we only enrolled 16 participants with 10 in the CFS group and 6 in the ME/CFS group. A larger group might have been able to distinguish a link between the symptom severity and mean RER.

Conclusions:

This study found ME/CFS and CFS participants high significantly elevated RER values compared to historical healthy controls. ME/CFS participants did not have an elevated RER compared to CFS participants. Symptoms of the diseases did not have any association with the increased RER values. Therefore, hypotheses 1 and 2 cannot be rejected while hypotheses 3 and 4 were rejected.

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