

Protocol for Submissions to CORIHS

TITLE: Sex differences in exercise-related post-exertional malaise in ME/CFS

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A. SPECIFIC AIMS

Specific Aim 1: After two high-effort six minute walk tests conducted on consecutive days, female subjects with ME/CFS as compared to male ME/CFS subjects will show slower recovery to resting baseline with respect to cardiac autonomic functioning (HRV, BP), physical functioning, and symptom resolution.

Specific Aim 2: Female subjects with ME/CFS as compared to males with ME/CFS will show greater adverse impact on autonomic and physical functioning and symptom severity after the day 2 exercise test.

B. BACKGROUND AND SIGNIFICANCE

Post-exertional malaise (PEM), i.e., prolonged symptom flare-ups lasting at least 24 hours after physical activity, is a debilitating symptom of chronic fatigue syndrome (CFS) experienced by many but not all patients. PEM appears to negatively impact both physical and cognitive abilities.

In the literature, patient reactions associated with PEM have included increased symptoms of pain and fatigue, [1–3] abnormal cardiopulmonary responses to exercise, [4, 5] decreases in physical activity behaviors, [2, 6, 7] changes in cognitive function [8, 9] and up-regulation of numerous biological variables. [10, 11] Although a number of studies have been conducted, consistent results and/or replication of findings have been rare. [12]

In addition, sex differences in heart rate variability (HRV) and blood pressure (BP), the key autonomic variables in this study, are more likely to be identified during exercise recovery (19, 20). These studies found slower exercise recovery in women with respect to both HRV and BP. Regarding ME/CFS patients, sex differences have been recently reported with respect to greater symptom severity and lower functioning in women vs. men (21) which may indicate a greater susceptibility to prolonged symptom flare-ups in women, as reflected in PEM (19). Thus, we hypothesize that the repeat exercise test protocol is more likely to reveal sex differences indicating higher PEM severity, greater autonomic imbalance, and slower recovery times in women as compared to men with ME/CFS.

C. PRELIMINARY STUDIES

Preliminary data (N=73) from the PI's laboratory indicated that self-report PEM scores at resting baseline (frequency x severity ratings of PEM) were positively correlated ($p < .05$) with fatigue ratings taken immediately after and 10 minutes after completion of a standard low exertion 6MWT. This indicates that participants' PEM scores at baseline are predictive of higher fatigue ratings following even a modestly effortful physical exertion task (in contrast to the high effort 6MWT proposed). In addition, fatigue scores at baseline increased at both 10- ($p = .013$) and 20-minutes ($p = .005$) after completion of the walk test. By comparison, in healthy subjects, the six minute walk test is associated with *lower* post-walk fatigue (18). Thus this preliminary data suggest that the abnormal symptom exacerbation characteristic of PEM can be provoked and confirmed by patients after a brief exercise task as proposed in this application.

In order to ensure PEM provocation, we are scheduling two high effort 6MWTs on consecutive days modeled after a recent protocol for 2 day maximal exercise testing in ME/CFS (8, 9). The study-scheduled day two test is intended to take advantage of the prolonged nature of PEM (1, 2) which lasts 24 hours or more (subjects will be screened for this symptom). Thus rather than recovering from the day 1 test by day 2, as would be the case with healthy individuals, PEM for the ME/CFS participants is expected to be even greater on day 2, providing another opportunity to assess exercise recovery abnormalities. Of particular interest is the

trajectory of potential sex differences during the post-exercise recovery period and its implications for biomarkers of illness status with possible implications for activity management.

D. RESEARCH DESIGN AND METHODS

1. Rationale/overview

The rationale for the proposed study is to identify abnormalities provoked by repeated knee squats (30 sec.) and six minute walk tests in individuals with CFS who report the symptom of post-exertional malaise.

2. Research Site

SBUH: Psychiatry department in the HSC.

3. Study sample

The study sample will consist of males and females with ME/CFS who report significant post-exertional malaise. We will conservatively assume a pre-enrollment withdrawal rate of 20% and an assumed 20% post-enrollment attrition rate. In order to achieve an endpoint sample of 32, the initial sample will be 40 (phone-screened) enrolled participants. About 5 new patients a month will be needed over the 8-month recruitment period to yield a baseline sample of 40 ME/CFS patients. Study ads will emphasize that the study will help to advance our understanding of ME/CFS.

4. Screening

Inclusion criteria: These are: patients aged 18-65 of both sexes who are considered physically capable of doing the exercise tasks and are willing to wear a heart monitor (10 min/day) and an actigraph (16 days; waking hours only). Subjects must also meet our validated phone-screen eligibility for ME/ CFS criteria (38; Appendix 1)) which will require the symptom of PEM. To assess patient-reported PEM during the phone screen, a PEM score will be obtained (frequency x severity of the symptom of PEM; pilot study (above)). Only those subjects with self-reported persistent presence of moderate to high intensity PEM lasting at least 24 hours will be study-eligible (>75% of ME/CFS subjects report long duration PEM; 2, 6). In addition, 3 out of 7 secondary symptoms of ME/CFS are required (apart from PEM), i.e., headaches, tender lymph nodes, sore throat, myalgias, arthralgias, sleep disturbance, and/or problems with memory or concentration. A physician note confirming a CFS diagnosis will be requested.

Medical exclusions as determined by the validated phone screen interview (14), will consist of cases of fatigue clearly attributable to self-report medical conditions such as untreated hypothyroidism, unstable diabetes mellitus, organ failure, chronic infections, and chronic inflammatory diseases, or AIDS. Exclusionary psychiatric disorders include any psychosis, or alcohol/ substance abuse within two years prior to illness onset and any time afterward, and current or past depression with melancholic or psychotic features within 5 years prior to onset of ME/CFS or anytime afterward (14). Self-report pregnancy is also an exclusion. Two other exclusionary criteria will be used: a) patients on heart medication or patients not dose-stabilized for at least 3 months on antidepressant drugs; b) patients at significant risk of suicide or in need of urgent psychiatric treatment. As much as possible, appropriate medical and psychiatric referrals to facilities local to subjects will be provided.

The structured screening phone interview was shown to be 98% reliable in the PI's previous study [14] in screening out exclusionary medical and psychiatric disorders in chronic fatigue evaluation when compared to subsequent study-based medical evaluations and clinical interviews using the Structured Clinical Interview for DSM-IV.

5. Procedures

To initially verify patient-reported post-exertional malaise (PEM) (or its absence), subjects will be asked several questions about their symptoms of PEM (frequency, duration, intensity) during the phone screen and a PEM score will be obtained (based on previous pilot data). Subjects with self-reported presence (lasting at least 24

hrs.) will be assigned to a physically exerting task. These repeat exertion tasks will ensure that PEM is triggered, a critical aspect of the study.

The physically exerting task will consist of the following: 30 sec. of knee squats followed by two six minute walk tests to generate PEM. Heart rate and blood pressure will be measured during these tests. These repeat exertion tasks will ensure that PEM is triggered, a critical aspect of the study. During the baseline week and the followup week, subjects will wear actigraphs (daytime hours) and heart monitors (10 min/day) and record their symptoms in an online diary. 27 females and 13 males will be initially enrolled.

Payment to Subjects

The total compensation to be paid for each participant will be up to \$100. Participants will be paid in installments as they complete each aspect of the study (baseline, exercise tests, follow-up) Participants will be paid \$50 for completion of the one-week baseline assessment (two six minute walking tests, questionnaires, activity and heart monitors). For the one-week follow-up, participants will be paid an additional \$50 for completion of the activity and heart monitors.

E. STATISTICS

Data analysis will be done with independent and paired t-tests, chi square, ANOVA, and Pearson correlations.

F. FUNDING STATUS, DETAILS

This study is fully funded by NIH.

G. HUMAN SUBJECTS RESEARCH PROTECTION FROM RISK

Risk to Subjects

Documentation of all study activities will be reviewed by the study staff to ensure the protocol is adhered to. Any significant adverse events will be documented and immediately reported to the PI.

Potential Benefits of Proposed Research to the Subjects and Others

There is no health benefit to subjects.

Importance of the Knowledge to be Gained

Participation will advance the understanding of chronic fatigue syndrome.

H. DATA SAFETY MONITORING PLAN (for more than minimal risk studies)

This study is minimal risk.

I. LITERATURE CITED

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