

Autonomic Physiology of Post-exercise Fatigue in Chronic Fatigue Syndrome

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A. Statement of study purpose and rationale

The purpose of this study is to determine whether abnormal hemodynamic and autonomic changes are associated with post-exertional fatigue in the chronic fatigue syndrome.

The chronic fatigue syndrome is a debilitating illness that is believed to result from either a viral agent or immunologic dysfunction. Affected individuals experience severe, activity-limiting fatigue of acute onset, lasting more than six months without identifiable etiology. Associated signs and symptoms include fever, chills, myalgias, arthralgias, sore throat, tender adenopathy, generalized muscle weakness, sleep disturbance, and postexertional fatigue.¹¹ Most objective assessments of aerobic and muscle function in chronic fatigue patients have suggested either normal or near normal capacity.²³⁴

An association between neurally-mediated syncope and chronic fatigue syndrome has recently been noted. A study of 23 patients with chronic fatigue syndrome revealed that 22 has positive tilt tests, as compared to only 4 of 14 controls. Moreover, their symptoms improved when therapy directed at neurally-mediated syncope was initiated.⁵⁵ These observations suggest an autonomic component to the fatigue that US patients experience.

One of the most universal and debilitating features of US is post-exertional fatigue. To determine whether post-exertional fatigue is associated with abnormal physiologic adaptation to exertion, we plan to compare hemodynamic, orthostatic tolerance, baroreceptor, and heart period variability responses to a maximal bout of treadmill exercise.

B. Description of study design and statistical analysis

We will recruit 10-30 patients with documented chronic fatigue syndrome and a similar number of age, sex, and weight matched controls. Individuals will report to the General Clinical Research Center between 0800 and 1100 for hospital admission. An initial history, physical exam, ECG and blood tests will be performed. A single peripheral IV will be placed, a Holter monitor will be applied, and a Ohmeda 2300 Finapres noninvasive finger cuff blood pressure monitor will be applied. Subjects will be quietly for ten minutes, followed by measurement of baroreceptor sensitivity by injection of a weight adjusted dose

¹ Buchwald D "Defining Chronic Fatigue Syndrome" in Straus SE, Chronic Fatigue Syndrome (1994) Marcel Decker, Inc. New York, NY. 45-60.

² Lane RJK Burgess AP, Flint J, Riccio K Archard LC. Exercise responses and psychiatric disorder in chronic fatigue syndrome. *BMJ* 1995; 311: 544-545.

³ Riley MS O'Brien CJ, McCluskey DR, et. al. Aerobic Work Capacity in patients with chronic fatigue syndrome. *BMJ* 1990; 301: 953-6.

⁴ Kent BraUn j, Sharma M Weiner MW, et.al. Central Basis of muscle fatigue in chronic fatigue syndrome. *Neurology* 1993; 43: 125-31.

⁵ Bou-Holaigah I, Rowe PC, Kan J, Calkins H. The Relationship Between Neurally-Mediated Syncope and the Chronic Fatigue Syndrome. *JAIM* 1995; 274: 961-967.

of phenylephrine. Subjects will be tilted to 60 degrees of head-up tilt on a motor-driven tilt table. Ten minutes of quiet hemodynamic measurements (heart rate, blood pressure) will be performed.

Subjects will then be transported to the Exercise Physiology Laboratory on PH9 for graded treadmill exercise testing using the Bruce protocol. Subjects will wear a mouthpiece and breathing valve during exercise. The $\dot{V}O_2$, $\dot{V}E$, respiratory exchange ratio, and minute ventilation will be continuously monitored. Following exercise, the patient will return to the General Clinical Research Center for follow-up evaluation. The Borg assessment of perceived exertion will be administered. At 1 hour post-exercise, subjects will lie quietly for ten minutes, followed by measurement of baroreceptor sensitivity by injection of a weight adjusted dose of phenylephrine. Subjects will be tilted to 60 degrees of head-up tilt on a motor-driven tilt table. Ten minutes of quiet hemodynamic measurements will be performed. This series of supine and tilt hemodynamic measurements will be repeated at 3, 6 and 24 hours post-exercise. Prior to each set of hemodynamic measurements, the Wood Mental Fatigue Inventory and the Activity Restriction Index will be administered,

Primary end-points will include degree of post-exercise fatigue induced as measured by the Wood's Mental Fatigue Inventory and the Activity Restriction Index, exercise induced changes in supine pulse and blood pressure, the degree of orthostatic intolerance following exercise as measured by pulse and blood pressure response to headup tilt, and the change in the baroreceptor sensitivity following exercise. Secondary end points will include exercise induced change in BF power (high frequency power, an index of parasympathetic activity, as determined by frequency domain analysis of heart period variability using the Fast Fourier Transform), exercise induced changes in LF/BF power ratio (low frequency/high frequency power, an index of sympathetic activity based on analysis of heart period variability), exercise induced changes in tilt-associated BF power and LF/BF power. Finally, catecholamine, neuropeptide Y, and lactate responses to exercise will be evaluated. Analysis of co-variance will be used to compare these exercise induced changes from baseline in the 2 groups for supine pulse, blood pressure, BF power, LF/BF ratio, baroreceptor sensitivity, pulse response to tilt, blood pressure response to tilt, BF during tilt, LF/BF during tilt, catecholamines, lactate, neuropeptide Y, Activity Restriction Index, and Wood's Mental Fatigue Inventory. Baseline (pre-exercise) values of pulse, blood pressure, and orthostatic/autonomic response to tilt (i.e. tilt associated changes in pulse, blood pressure, HF power and LFW power) will be compared using a Student's T-test. Analysis of variance (ANOVA) will be used to compare post-exercise serial hemodynamic and autonomic measures including supine pulse, blood pressure, HF power, and LF/HF power; tilt-induced change in pulse, blood pressure, HF and LFW power; baroreceptor sensitivity, serum lactate, catecholamine and neuropeptide Y levels.

C. Description of study procedures

a. Peripheral IV placement

i. Baroreceptor Sensitivity

Phenylephrine will be injected as an intravenous bolus in the dosage of 2 micrograms per kilogram. Immediately following phenylephrine injection, the slope of the line relating RR interval and systolic blood pressure will be calculated. Six consecutive measurements will be taken and the mean value reported.

ii. Tilt testing

Tilt testing will be performed on a motorized table, which will be driven from supine position to 60 degrees head-up tilt for 10 minutes duration. Heart rate and blood pressure will be monitored continuously and noninvasively.

iii. Heart Period Variability Analysis

Holter ECG recordings will be digitized on a Marquette Model 8000 Holter scanner located in the Research Holter Laboratory (P&S 9405). Each QRS complex will be scanned and classified as normal or abnormal. The type and time of occurrence for each QRS complex will be transferred to a SUN 4n5 microcomputer. Additional editing will occur prior to calculation of the power spectra by a Fast Fourier Transform algorithm. Low and high frequency power are determined by performing an integral over the

frequency ranges 0.03-0.15 Hz and 0.15-0.40 Hz, respectively. All IHF and LF values are reported following natural log transformation.

iv. Exercise Testing

Exercise testing consist of graded intensity treadmill exercise in accordance with the Bruce protocol. A mouthpiece and breathing valve will be applied for continuous measurement of oxygen consumption, carbon dioxide production, respiratory exchange ratio, and minute ventilation. Heart rate and cardiac rhythm will be continuously monitored. Blood pressure will be monitored periodically using a non-invasive cuff. The criteria for a maximal test will include: a plateau in the V_{O2} while the work rate continues to rise, a respiratory exchange ratio of at least 1.10, a leveling of heart rate, and attainment of age predicted maximal heart rate (220-age + 10 bpm).

v. Phlebotomy

Three tubes of venous blood will be drawn peripherally at the time of each set of hemodynamic measurements. A total of 5 blood draws will be required over the course of 24 hours.

D. Study drugs

Phenylephrine in intravenous bolus doses of 2 microgram per kilogram will be administered for baroreceptor sensitivity measurement. No other drugs will be used in this study.

E. Medical Devices

No medical devices will be used.

F. Study Questionnaires

The following questionnaires will be administered for assessment of patients symptoms: the Wood Mental Fatigue Inventory⁶, the Activity Restriction Index⁷, and the Borg scale of perceived exertion.⁸

G. Description of study subjects and method of recruitment

The study subjects will include patients who meet the CDC diagnostic definition for chronic fatigue syndrome. Patients referred to the syncope center for tilt testing will be solicited. In addition, CPMC providers caring for patients with chronic fatigue syndrome will provide referrals. Controls will be solicited from the students and employees at CPMC and Columbia University. In addition, a newspaper ad may be used to recruit further control subjects.

H. Confidentiality of the study

Information regarding participation and individual results of this study will be kept strictly confidential. Data will be reported in an anonymous manner only.

I. Location of study

⁶ Bentall Rp, Wood GC, Marrinam T, Dears C, Edwards RHT. A brief mental fatigue questionnaire. *Be J Chn Ps)chol* 1993; 32: 375-9.

⁷ Lane RJK Burgess AP, Flint J, Riccio K Archard LC. Exercise responses and psychiatric disorder in chronic fatigue syndrome. *BMJ* 1995; 311: 544-545.

⁸ Borg G. Perceived exertion as an indicator of somatic stress, *ScandJRehab Med* (1970) 23: 92-93.

The application of Holter monitors, tilt testing, baroreceptor testing, and hospitalization for the duration of the study will take place at the General Clinical Research Center. Exercise testing will be performed in the Exercise Physiology Laboratory on PH9.

J. Risks and benefits

The risks associated with this study include the following:

- *IV catheters* A small amount of bleeding and discomfort may occur during insertion of the peripheral IV catheter. In addition, there is a small chance of infection at the site of the IV catheter, however, this risk should be minimal due to the fact that catheters will remain in place for only approximately 24 hours.
- *Phlebotomy*: There is small chance of minor bleeding and/or irritation at the site of blood drawing.
- *Tilt Testing*: Tilt-testing will be performed under the supervision of an M.D. who is familiar with tilt testing. Safety strap will be used to prevent subjects from falling off the table. Tilt testing may cause a decrease in blood pressure and/or fainting during upright posture. While this risk may be greater in individuals with chronic fatigue syndrome or a prior history of syncope, however, the duration of tilt during each phase of this study is much shorter (10 minutes) than the mean time at which fainting occurs. No provocative pharmacologic agent will be used.
- *Holter monitor*: The only risks associated with use of the Holter monitor is mild irritation at the site of electrode placement. However, the tape used is hypoallergenic and the rate of adverse reactions is less than 2% over a 24 hour period.
- *Exercise Testing*: The risk of exercise testing is approximately 0.5 deaths per 10,000 tests in large heterogeneous populations who undergo exercise testing. Additional data suggests that exercise testing in individuals without known or suspected cardiac disease, such as the subjects in this study, is associated with even lower risks.⁹
- *Baroreceptor Sensitivity*: The phenylephrine used in doses of approximately 2 ug/kg produce a small (less than 30 point) rise in systolic blood pressure and a small 10-20 point decrease in pulse rate. The medication has been used safely for many years in this fashion. The most common side effects include a slowing of heart rate, restlessness, and rarely, ectopic heart beats or transient Mobitz I heart block. The effects of intravenous phenylephrine resolve in less than 2 minutes.

Benefits to CFS patients who participate will include facilitating a better understanding of their disease complex, which may lead to new therapeutic initiatives aimed at treating chronic fatigue syndrome. In addition, these subjects may be included in future therapeutic trials conducted by our group in the future. No direct medical benefits are anticipated for control subjects, however controls will be compensated for their time and cooperation with a \$100 check. All study subjects will undergo five examinations and diagnostic testing by a physician, and the possible benefit of detecting occult cardiovascular disease exists.

K. Alternative therapies

There are no therapies involved in this study.

L. Compensation and costs to subjects

⁹ American College of Sports Medicine: Guidelines for Exercise Testing and Prescription. Philadelphia: Lea & Febiger, 1991: 5.

Subjects will not receive monetary compensation for this study. Normal controls will receive \$100.00 as a compensation for their participation. Mstories, physical exams, Holter recordings, tilt testing, ECG, echocardiograms, exercise testing, and blood testing will be done free of charge.

M. Minors and research subjects

No minors (under 18) will be studied.

N. Radiation and radioactive substances

No radiation or radioactive substances will be used in this study.