1-1-2011

Using cardiopulmonary exercise testing to evaluate fatigue and post-exertional malaise in ME/CFS

Christopher R. Snell
University of the Pacific, csnell@pacific.edu

Staci R. Stevens
IACFS/ME

Todd E. Davenport
University of the Pacific, tdavenport@pacific.edu

J. Mark VanNess
University of the Pacific, mvanness@pacific.edu

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Chris Snell is scientific director of the Pacific Fatigue Laboratory, and chairs the federal Chronic Fatigue Syndrome Advisory Committee (CFSAC). He was one of the presenters at the recent state of knowledge workshop organised by the NIH.

Christopher R. Snell, PhD1,2; Staci R. Stevens, MA2; Todd E. Davenport, DPT, OCS2,3; J. Mark Van Ness, PhD1,2

1 Department of Sport Sciences, University of the Pacific, 3601 Pacific Avenue, Stockton, CA 95211, USA

2 Pacific Fatigue Laboratory, 3601 Pacific Avenue, Stockton, CA 95211, USA

3 Department of Physical Therapy, Thomas J. Long School of Pharmacy and Health Sciences, 3601 Pacific Avenue, Stockton, CA 95211, USA

The absence of reliable diagnostic laboratory tests or biomarkers presents significant problems for persons with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), treating physicians, and the ME/CFS research community alike. Typically ME/CFS diagnoses rely on self-report measures where patients describe the extent and duration of their fatigue and attendant symptoms either verbally or on a questionnaire.

An alternative to the current binary approach (i.e., fatigue or no fatigue) or use of paper and pencil inventories for evaluation of symptoms in ME/CFS is to employ direct, objective multi-system, measures of physical function that may also provide insights to the underlying pathophysiology of fatigue in ME/CFS. One such methodology is cardiopulmonary exercise testing (CPET). With a long history of use by exercise physiologists in research settings, this non-invasive, integrative assessment approach is now increasingly endorsed for the clinical evaluation of undiagnosed exercise intolerance and for the objective determination of functional capacity and impairment.[1]

An early definition conceptualizes fatigue as reduced efficiency after doing work.[2] CPET is uniquely able to quantify this reduction in efficiency with measures of both workload and the metabolic cost of that work. Additionally, other available cardiovascular, pulmonary and symptom data further enhance the value of CPET for diagnostic, clinical and research purposes.

As a corollary to extreme fatigue, post-exertional malaise (PEM) or exacerbation of symptoms following physical exertion, is considered one of the most common and recognizable aspects of ME/CFS. For the objective assessment of PEM, CPET has the advantage of serving as both an indicator of clinical status and a quantifiable model of physical exertion.

The principles underlying CPET are simple. Physical exertion requires that the cardiovascular system supply oxygen (O2) to active muscles and the pulmonary system remove carbon dioxide (CO2) from the blood. Taxing these systems has the capacity to reveal abnormalities that may not be apparent at rest and thus elucidate the mechanisms underlying exercise intolerance in ME/CFS. Procedures for CPET are widely available [1] as are results profiles for a variety of disabling conditions. [3] These data can facilitate differential diagnosis to rule out conditions that could otherwise explain patient symptoms.

CPET is generally performed using a motorized treadmill or stationary cycle ergometer. For reasons of safety, the cycle is preferable when testing ME/CFS patients. Possible orthostatic intolerance and the extreme exhaustion patients usually experience post-testing can make using a treadmill particularly hazardous. Individualized ramp protocols, which involve

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only modest increases in work rate per stage should be used and tailored to yield a fatigue-limited exercise duration of 8 to 12 minutes. Longer durations may result in patients terminating exercise because of specific muscle fatigue or orthopedic factors rather than cardiopulmonary end points. An important consideration for ME/CFS is to begin the test at a very low workload. Starting at too high a level will make for a very short test with results that are difficult to interpret. Test durations of less than 6 minutes may not show a linear relationship between oxygen consumption and work-rate. [1]

Some of the key measures available from CPET include: maximal aerobic capacity (Peak VO2 or VO2 max); ventilatory or anaerobic threshold (VT); and peak respiratory exchange ratio (RER). In addition to these gas exchange variables, workload at any given point and, with the integration of electrocardiography, key indicators of cardiovascular dynamics can also be measured.

Often synonymous with functional capacity or exercise tolerance, Peak VO2 defines the physiological limits of an individual. However it is important to note that when such terms are used to describe performance on activities like timed-walk tests, or the commercial functional capacity assessments often used to evaluate disability, these are only estimates of aerobic capacity which tend to overpredict VO2 .[1] CPET is required for precise measurement of functional capacity.

Most activities of daily living (ADL) are performed at levels below peak. VT is an important index of submaximal exercise capacity. It denotes the point at which energy production transitions from primarily aerobic to increasingly anaerobic glycolosis and is a crucial measure in CPET as it represents the onset of fatigue. Due to a lack of oxygen in the working muscle cells, work intensity cannot be maintained resulting in the reduction or cessation of activity. It may also be central to understanding the activity limitations in ME/CFS. If VT occurs at very low levels of oxygen consumption and/or at very low workloads, then even normal ADL may exceed the VT threshold. It is possible therefore that in ME/CFS the increased stress of requiring a greater anaerobic energy contribution even for normal ADL precipitates the symptom exacerbation seen in PEM. CPET provides the only way to non-invasively assess this significant transition point in energy metabolism.

Assessment of subject effort might be considered essential to interpreting any measure of physiological function. Exclusive to expired gas analysis, RER is defined as the ratio between inspired O2 and expired CO2. As exercise intensity increases the volume of CO2 begins to exceed that of O2. A ratio of CO2 to O2 greater than 1.10 is considered an indicator of excellent effort during an exercise test .[1] As an accurate and reliable indication of subject effort, RER substitutes for age-predicted maximal heart-rate values in this respect. Variability of 10-15 beats per minute can be expected within an age group which complicates interpretation of results where percentage of predicted maximal heart rate is the exercise endpoint.[4] There are also difficulties posed by use of pharmacological agents [1] and the cardiovascular abnormalities seen in ME/CFS.[5] Problems of response bias in self-report indictors of effort are also averted.

Because RER permits accurate comparison of subject effort across serial exercise tests, it should be of prime consideration for any clinical intervention trial with functional endpoints.[1] CPET data including RER also allow for the more reliable interpretation of results when an exercise challenge is used to elicit symptoms as part of ME/CFS research studies. As a quantifiable measure of both physiological stress and effort, CPET enables direct comparison between patients and controls on these critical measures. This may be particularly

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relevant to research looking at immune function where individual fitness levels and exercise intensity can profoundly affect the immune response.[6]

The availability of RER also gives CPET the capacity to objectively document PEM in ME/CFS patients. The reproducibility of both metabolic and work intensity measures obtained through CPET is well documented.[1] But research using CPET to examine functional capacity in CFS has found that a single test may be insufficient to identify abnormalities in work performance among CFS patients.[7, 8] By employing a dual test paradigm (i.e., 2 exercise tests, each separated by 24 hours) it is possible to compare data across tests. A significant change in exercise capacity during follow-up testing with similar peak RER values, it could be argued, is clear evidence of PEM. It should also be noted that RER is a critical arbiter when dealing with accusations of malingering or lack of effort!

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ME FACTS

From over 2,000 pages of information obtained under the Freedom of Information Act, much is already known about the design and progress of the PACE Trial, including the fact that its entry criteria were intentionally broad (*"We chose these broad criteria in order to enhance generalisability and recruitment";* Trial Identifier 3.6).

Despite the use of such broad entry criteria, there were serious recruitment difficulties, so the entry criteria were broadened even further when on 14th July 2006 Peter White sought approval from the West Midlands MREC to write to GPs imploring them to send anyone with "*chronic fatigue (or synonym)*" for entry into the PACE Trial, thereby opening the trial to anyone who was merely chronically tired.

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