

Exercise Pathophysiology in ME/CFS & Long COVID

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Systematic Analysis, Review and Summary

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Run by Claude 4.6

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50

STUDIES REVIEWED

2003–2026

TIME SPAN

32

2-DAY CPET STUDIES

6

META-ANALYSES / REVIEWS

5+

PROPOSED MECHANISMS

§ 1

Overview & Corpus Description

This analysis synthesizes 50 peer-reviewed studies published between 2003 and 2026 examining exercise pathophysiology in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and, in more recent years, Long COVID / Post-Acute Sequelae of SARS-CoV-2 (PASC). The corpus spans foundational single-CPET studies, consecutive two-day CPET protocols, invasive hemodynamic investigations, molecular and omics analyses, neuroimaging, and two formal meta-analyses.

The body of evidence has matured substantially over two decades. Early studies (Studies #1–6, 2003–2013) established that single-day exercise tests failed to capture the characteristic abnormality of ME/CFS, while consecutive two-day CPET protocols (introduced prominently around 2007, Study #2) became the defining methodological advance. Post-2020 literature increasingly integrates molecular mechanisms (proteomics, metabolomics, transcriptomics, microbiome) and extends findings to Long COVID populations.

"A single exercise test is insufficient to demonstrate functional impairment in CFS patients. A second test may be necessary to document the atypical recovery response and protracted malaise unique to CFS." — VanNess et al., 2007 (Study #2)

The studies employ diverse but overlapping diagnostic criteria: Fukuda/CDC (1994), Canadian Consensus Criteria (CCC, 2003), International Consensus Criteria (ICC, 2011), SEID criteria (IOM report, 2015), and WHO Long COVID definition (2022). Several studies require post-exertional malaise (PEM) as a mandatory inclusion criterion regardless of formal diagnosis label.

Two-Day CPET: The Core Objective

Finding

The most replicated and clinically significant finding across this corpus is the failure to reproduce cardiopulmonary exercise performance on a second consecutive-day CPET. This is present across all major ME/CFS diagnostic criteria and constitutes the strongest objective biomarker of PEM available to date.

Consistently Documented Decrements on Day 2

<p>Peak VO₂</p> <p>Significant decline in maximum oxygen consumption on Day 2 in ME/CFS; controls reproduce or improve. Documented in Studies #2, 3, 6, 8, 13, 16, 22, 23, 29, 36, 38, 44, 49.</p>	<p>Workload at VAT</p> <p>Work rate at the ventilatory anaerobic threshold shows the largest effect sizes. Both meta-analyses (#25, #30, #36) confirm highly significant group × test interaction.</p>
<p>O₂ Pulse</p> <p>Reduced O₂ pulse (stroke volume × O₂ extraction proxy) on Day 2, implicating both cardiac output and peripheral extraction deficits (Studies #38, #44).</p>	<p>Heart Rate & RPP</p> <p>Reductions in HR, rate-pressure product, and blunted chronotropic response documented in Studies #15, #32, #44, suggesting autonomic dysregulation.</p>

Meta-Analytic Confirmation

Three meta-analyses directly address the two-day CPET evidence base:

- Lim et al. 2020 (Studies #25, #30): Pooled data confirm overall mean values of all CPET parameters are lower on Day 2 for ME/CFS; workload at VT shows the greatest differential (−10.8 Day 1 vs. −33.0 Day 2 versus controls, $p < 0.05$).
- Franklin & Graham 2022 (Study #36): Clinically significant test-retest reduction in work rate at anaerobic threshold in ME/CFS compared to healthy controls; largest systematic review of this question.

Diagnostic Sensitivity

Nelson et al. 2019 (Study #13) quantified that a 6.3–9.8% decrease in work rate at VT on Day 2 may serve as a diagnostic biomarker. Snell et al. 2013 (Study #6) demonstrated 95.1% overall classification accuracy distinguishing ME/CFS from controls using Day 2 CPET data via multivariate analysis — results that were near-chance on Day 1 alone.

Recovery Duration

Moore et al. 2023 (Study #39) quantified recovery from a two-day CPET: ME/CFS subjects required an average of **~14 days** to recover, compared to approximately **2 days** for sedentary controls — providing the first direct quantification of PEM duration following standardized exertional challenge.

Reliability of CPET Measures

Davenport et al. 2020 (Study #21) established that CPET measurements demonstrate moderate-to-high reliability in ME/CFS, with moderate-to-large effect sizes versus controls, validating the protocol for research and disability assessment. Larson et al. 2019 (Study #17) confirmed that individuals with MS and HIV reproduced CPET measures, while neither ME/CFS participant did — underscoring the diagnostic specificity of the day-2 decrement.

Proposed Biological Mechanisms

Multiple, non-mutually-exclusive mechanisms have been identified or proposed across the corpus. A convergent picture implicates a cascade originating in impaired peripheral oxygen delivery and mitochondrial bioenergetics, amplified by immune dysregulation and autonomic dysfunction.

- 1 Impaired Peripheral Oxygen Extraction** CPET HEMODYNAMIC
- Vermeulen et al. 2014 (Study #7) demonstrated low muscle O₂ uptake despite elevated cardiac output relative to VO₂ — inconsistent with simple deconditioning. Systrom et al. (Study #27, invasive CPET) identified two neurovascular patterns: depressed cardiac output from impaired venous return, and impaired peripheral O₂ extraction. Melamed et al. 2019 (Study #18) further characterized a cohort with isolated systemic oxygen extraction failure, implicating intrinsic skeletal muscle mitochondrial pathology or microcirculatory dysregulation. Thomas et al. 2026 (Study #50) showed that tissue saturation index (TSI%) in Long COVID normalized to resting levels far earlier during exercise than in controls, and worsened on Day 2, providing near real-time evidence of impaired muscle oxygenation.

- 2 Mitochondrial & Bioenergetic Dysfunction** METABOLISM OMICS
- Vermeulen et al. 2010 (Study #4) showed patients reaching anaerobic threshold and peak exercise at far lower O₂ consumption than controls, worsening on Day 2, implying increased reliance on anaerobic glycolysis and reduced mitochondrial ATP production. Lien et al. 2019 (Study #16) documented abnormal blood lactate accumulation during repeated exercise in ME/CFS (rising) compared to controls (decreasing) – a biochemical signature of failed metabolic adaptation. Haunhorst et al. 2024 (Study #45) synthesized evidence that dysfunctional mitochondria and microcirculation, maintained by latent immune activation, conjointly impair peripheral bioenergetics. Germain et al. 2022 (Study #35) via plasma metabolomics found over a quarter of identified pathways differing uniquely during 24-hour recovery in ME/CFS, with disruptions centring on glutamate metabolism.

3 Autonomic Nervous System Dysregulation

Joseph et al. 2022 (Study #37) demonstrated in a randomised placebocontrolled trial that pyridostigmine (an acetylcholinesterase inhibitor) improved peak VO₂ in ME/CFS by increasing cardiac output and right ventricular filling pressures, with the placebo arm potentially triggering PEM onset – directly implicating treatable neurovascular dysregulation. Davenport et al. 2019 (Study #15) documented chronotropic intolerance – abnormally blunted heart rate responses at both maximal and submaximal exercise – as a common, overlooked feature. Van Campen & Visser 2021 (Study #28) showed that orthostatic intolerance in ME/CFS is not explained by deconditioning (normal peak VO₂ was compatible with severe orthostatic abnormalities), with all ME/CFS patients showing abnormal cerebral blood flow decline during orthostatic stress.

4 Immune Dysregulation & Inflammation

Vu et al. 2024 (Study #43, single-cell transcriptomics) identified immunological defects at baseline and improper platelet activation post-exercise in ME/CFS, with minimal immune changes elsewhere – suggesting platelet dysfunction as a specific exercise-induced pathway. Germain et al. 2025 (Study #48, proteomics) found postexercise suppression of T and B cell signalling, downregulation of IL-17 pathways, upregulation of glycolysis/gluconeogenesis – consistent with mitochondrial stress and impaired immune recovery. Bouquet et al. 2019 (Study #14, transcriptomics) found only 6 differentially expressed genes despite clear functional deterioration, suggesting the molecular signature is subtle or highly regulated. Thomas et al. 2025 (Study #46, Long COVID) provided first evidence of exercise-induced microclot fragmentation triggering systemic inflammation – a mechanism potentially underlying exercise-induced symptom exacerbation in Long COVID.

5 Microbiome & Gut Permeability Alterations

Shukla et al. 2015 (Study #9) showed significant changes in gut bacterial phyla abundance following exercise in ME/CFS not seen in controls, plus delayed clearance of bacteria from blood – suggesting exercise-induced gut permeability and systemic translocation as contributors to post-exertional symptoms. Giloteaux et al. 2016 (Study #10, identical twins) found evidence of dysfunctional immune activation post-exercise and suggested prokaryotic viruses may

contribute to mucosal inflammation and dysbiosis.

NEUROSCIENCE

6 **Central Nervous System & Serotonergic Dysregulation**

Georgiades et al. 2003 (Study #1) – the earliest study in the corpus – identified significant differences between ME/CFS patients and controls in CNS serotonergic and dopaminergic modulators, suggesting central neural mechanisms contribute to the perception of effort and impaired exercise tolerance. This sets a foundation for the neuroimaging work that follows two decades later.

NEUROPATHOLOGY

7 **Small Fibre Neuropathy & Microvascular Shunting**

Joseph et al. 2021 (Study #27, invasive CPET) found that in ME/CFS patients with small-fibre pathology, neuropathic dysregulation causing microvascular dilation may limit exertion by shunting oxygenated blood away from capillary beds, reducing cardiac return. Christian et al. 2025 (Study #47, case report) demonstrated reduced blood flow to the head during a PEM episode, with a novel in-ear device showing promise as a monitoring tool.

METABOLISM

8 **Elevated Resting Lactate as Risk Marker**

Ghali et al. 2019 (Study #19) found that elevated blood lactate at rest correlates with PEM severity – suggesting some patients are in a state of baseline metabolic insufficiency that predisposes to more severe post-exertional deterioration. This is consistent with the bioenergetic failure model and suggests resting lactate as a potential clinical stratification tool.

GENOMICS

9 **Circular RNA & Molecular Dysregulation**

Cheng et al. 2023 (Study #42) reported the first circRNA profiling study in ME/CFS across a two-CPET protocol. Specific circular RNAs showed differential expression at different timepoints pre- and postexercise, with enriched Gene Ontology terms implicating host genes relevant to ME/CFS pathophysiology – a novel molecular layer that warrants further investigation.

Neurological & Brain Findings

A distinct cluster of 6 studies (Studies #20, #26, #31, #33, #34, #47) investigates the neural correlates of PEM using fMRI and related neuroimaging. This represents a coherent sub-field within the corpus.

Default Mode Network Activation

Rayhan & Baraniuk 2021 (Study #31) demonstrated that submaximal exercise provokes increased activation of the anterior Default Mode Network (DMN) in ME/CFS during resting state — the opposite of the typical exercise-induced DMN deactivation seen in healthy individuals. This post-exertional DMN hypersensitivity is proposed as a neuroimaging biomarker of PEM.

Midbrain Ascending Arousal Network

Baraniuk et al. 2022 (Studies #33, #34) identified the midbrain ascending arousal network nuclei as key contributors to PEM. Critically, exercise caused *increased* activation in ME/CFS but *decreased* activation in Gulf War Illness (GWI) — indicating divergent pathophysiological mechanisms despite symptom overlap. This discriminative pattern has diagnostic potential.

Machine Learning Classification

Provenzano et al. 2020 (Study #20) applied logistic regression to fMRI data and achieved 80.9% diagnostic accuracy distinguishing ME/CFS from sedentary controls before exercise, with 76.1% accuracy during the PEM period — demonstrating that objective neural signatures of ME/CFS are detectable and worsened by exertion.

Operculo-Insular & Dorsal Midbrain Changes

Washington et al. 2020 (Study #26) found exercise-specific increased activation in ME/CFS in the dorsal midbrain, leg operculo-insular cortex, and right middle insula — regions emerging only post-exercise and therefore representing neural substrates of cognitive PEM. These findings offer a complementary neural signature to the cardiopulmonary data.

ME/CFS and Long COVID: Convergence of Evidence

Six studies in the corpus directly address the relationship between ME/CFS and Long COVID (Studies #41, #45, #46, #49, #50, and partially #40). This is the most rapidly expanding area of the field.

Overlapping CPET Profiles

Davenport et al. 2026 (Study #49, preprint) found no significant differences in bioenergetic failure between ME/CFS and Long COVID on two-day CPET – both show functionally equivalent impairment unexplained by hemodynamic or ventilatory changes.

Shared Exercise Derangements

Joseph et al. 2023 (Study #41) systematically reviewed the overlap: both conditions show ventilatory inefficiency, Day-2 VO_2 decrement, neurovascular dysregulation with impaired preload and peripheral O_2 extraction, and autonomic dysfunction.

Microclot Mechanism (Long COVID-specific)

Thomas et al. 2025 (Study #46) identified exercise-induced microclot fragmentation and systemic inflammation in Long COVID – raising serious concerns about exercise-based rehabilitation approaches

Tissue Oxygenation (Long COVID)

Thomas et al. 2026 (Study #50) demonstrated worsening TSI% responses on Day 2 in Long COVID, with rapid normalization suggesting impaired muscle oxygenation and recovery – directly paralleling ME/CFS findings.

"ME/CFS and Long COVID both involve a functionally significant bioenergetic failure complicated by inadequate post-exertional recovery, which is similar between the conditions and unexplained by hemodynamic and ventilatory changes." — Davenport et al., 2026 (Study #49)

The convergence of findings raises the possibility that Long COVID, at least the PEM-dominant subtype, represents a condition mechanistically indistinguishable from ME/CFS by current objective measures. The overlap has significant implications for clinical management: interventions harmful or ineffective for ME/CFS (notably graded exercise therapy as sole treatment) may carry equivalent risks in Long COVID.

Sex, Severity & Subgroup Effects

Sex Differences

Davenport et al. 2026 (Study #49) found that females exhibited more pronounced bioenergetic abnormalities and significant group-by-test effects on two-day CPET. Germain et al. 2025 (Study #48) identified distinct proteomic molecular responses between females and males following exertion in ME/CFS, underscoring sex as a critical biological variable. VanNess et al. 2010 (Study #3) established PEM as a real and incapacitating condition specifically in women, with distinctively different exercise responses from sedentary female controls.

Disease Severity

Van Campen et al. 2020 (Study #22) demonstrated that disease severity *negatively* correlates with exercise capacity in female ME/CFS patients, and that the Day 1→Day 2 deterioration in peak workload is **largest in the severe subgroup** — suggesting the two-day CPET protocol is not only diagnostic but also sensitive to severity gradation. Keller et al. 2024 (Study #44) confirmed that CPET-2 data signal more severe functional impairment than CPET-1, consistent with this dose-response relationship.

Male-Specific Confirmation

Van Campen et al. 2020 (Study #23) and 2021 (Study #29) confirmed that male ME/CFS patients show similar Day-2 decrements to females, with ME/CFS males showing clear deterioration while idiopathic chronic fatigue (ICF) males do not — validating both the sex-generalisability of the finding and its diagnostic specificity for ME/CFS versus overlapping fatigue conditions.

Deconditioning as Confounder: Ruled Out

Multiple lines of evidence converge on ruling out deconditioning as a primary explanation:

- Keller et al. 2024 (Study #44): abnormal post-exertional responses persisted when ME/CFS was matched with controls for aerobic capacity.
- Vermeulen et al. 2014 (Study #7): elevated cardiac output relative to O₂

uptake is the opposite of the deconditioning pattern.

- Van Campen & Visser 2021 (Study #28): orthostatic intolerance present in all ME/CFS patients regardless of %peak $\dot{V}O_2$.
-

Diagnostic Criteria Used Across Studies

CRITERIA	STUDIES USING	NOTES
Fukuda / CDC 1994	#1, 2, 3, 4, 5, 6, 7, 9, 11, 12, 14, 20, 23, 24, 26, 32, 34, 38, 40	Most widely used. Does not mandate PEM. Several authors add PEM requirement.
Canadian Consensus Criteria (CCC 2003)	#8, 10, 11, 16, 17, 19, 21, 23, 25, 35, 39, 44, 48	Requires PEM. Considered more specific. Used in most omics studies.
International Consensus Criteria (ICC 2011)	#10, 11, 12, 21, 22, 23, 28, 29, 32	Strictest criteria. Requires neurological, immunological, and energy symptoms.
SEID / IOM 2015	#12, 27, 41	Emphasizes PEM, unrefreshing sleep, cognitive impairment. Widely accepted.
WHO Long COVID 2022	#50	Only applicable to Long COVID studies.
PEM-only / Unspecified	#43, 47, 49	Some recent studies use PEM as the primary inclusion criterion regardless of label.
Meta-Analyses (multiple criteria)	#25, 30, 36	Include studies across multiple criteria sets.

A notable limitation across the corpus is heterogeneity in diagnostic criteria. Studies using Fukuda criteria alone may include patients without true PEM, potentially diluting effect sizes. Studies requiring PEM (CCC, ICC, SEID) consistently show larger and more reproducible findings. (See references for more details)

Limitations & Methodological Notes

Diagnostic Heterogeneity

Variable criteria across studies complicate pooled effect size estimates and may introduce patient heterogeneity.

Preprint Studies

Studies #46 (Thomas 2025) and #49 (Davenport 2026) are preprints not yet peer-reviewed – findings should be weighted accordingly.

Control Selection Bias

Some studies use sedentary controls rather than age/fitness-matched controls, potentially inflating between-group differences. Keller et al. 2024 specifically addressed this with aerobic-capacity matching.

Causality vs Association

Most studies are observational or cross-sectional post-exertional designs. The pyridostigmine RCT (Study #37) is a rare exception demonstrating mechanistic causality (neurovascular dysregulation).

Predominantly Female Samples

Most studies have majority-female cohorts reflecting disease epidemiology, but limiting male-specific generalisability until recent studies (#23, #29) explicitly addressed this gap.

Single-Centre Dominance

Several research groups (Stevens/VanNess/Davenport/Snell; Keller/Hanson; Van Campen/Visser; Baraniuk) generate a large share of the corpus – replication by independent groups is growing but remains limited.

Omics Studies: Sample Size

Molecular studies (metabolomics, proteomics, transcriptomics) are typically performed in small cohorts (n=10-40), limiting statistical power and generalisability.

Small Sample Sizes

Many individual studies are underpowered. The largest 2-day CPET study (Keller et al. 2024) is explicitly noted as the field's largest to date, yet remains modest by epidemiological standards.

Conclusions & Clinical Implications

Across 50 studies spanning over two decades, a robust and internally consistent evidence base has been assembled establishing the following conclusions:

- 1. PEM is a real, measurable, and pathological phenomenon.** The failure to reproduce cardiopulmonary exercise performance on consecutive-day CPET is the most replicated objective finding in ME/CFS research. It is statistically significant, clinically meaningful (95%+ diagnostic classification accuracy), and reproducible across laboratories and continents.
- 2. The mechanism is multi-systemic, not deconditioning.** Evidence from invasive CPET, metabolomics, proteomics, immunology, and microbiome studies converges on impaired peripheral oxygen extraction, mitochondrial bioenergetic failure, immune dysregulation, autonomic dysfunction, and microvascular abnormality – not simple physical deconditioning or psychological origin.
- 3. Long COVID and ME/CFS are pathophysiologically convergent.** Two-day CPET reveals statistically equivalent bioenergetic impairment in both conditions. The microclot and tissue oxygenation data raise urgent questions about exercise-based rehabilitation protocols for Long COVID.
- 4. The two-day CPET is a validated objective measure for PEM and functional impairment.** It has demonstrated reliability, discriminative validity, sensitivity to severity, sex-generalisability, and translational utility for disability assessment and treatment trials.
- 5. Clinical and research implications demand caution with exercise prescription.** The evidence from microclot fragmentation, worsening bioenergetics on Day 2, and prolonged (~14-day) recovery following standardized testing strongly argues against unmodified graded exercise therapy and supports energy envelope management and pacing approaches.

Analysis of 50 studies · ME/CFS & Long COVID Exercise
Pathophysiology · Studies #1 (2003) through #50 (2026) ·
Compiled April 2026

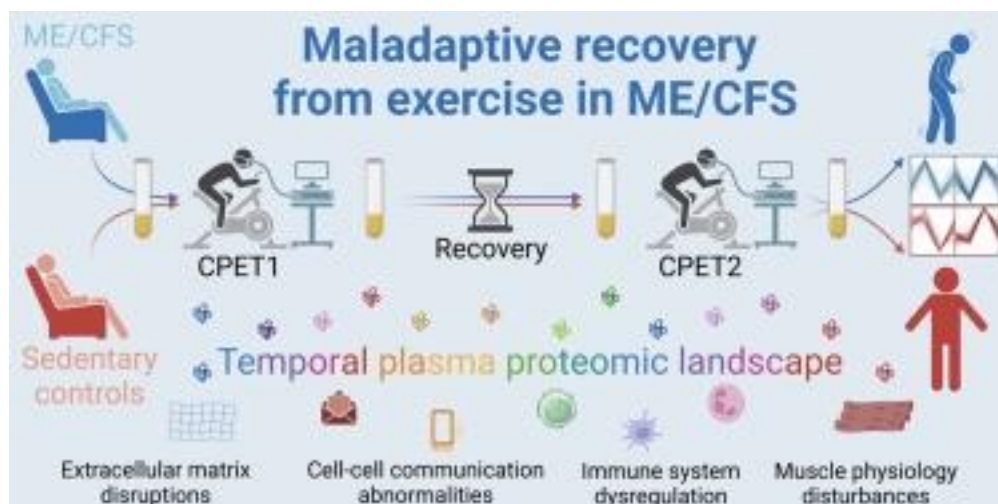
Study references

Description

- 50 Impaired peripheral oxygen delivery during submaximal exercise in adults with long COVID**
Callum Thomas, Ruth E. Ashton, Rebecca Owen, Ethan McNeil-Angopa, Jack Carr, Thomas Bewick, Mark A. Faghy
Physiological Reports Volume 14, Issue 8 e70873 First published: 23 April 2026
<https://doi.org/10.14814/phy2.70873>
Conclusion/Main finding: «CPET outcomes demonstrated impaired physical function on day 2 compared with day 1 for the LC cohort at rest and VT1. LC tissue saturation index (TSI%) remained elevated above rest for a shorter duration of exercise compared to CON on day 1 (2nd minute vs. 5th minute). On day 2, this response worsened for LC (Rest vs. 1st exercise minute: $63 \pm 5\%$ vs. $65 \pm 5\%$; $p < 0.05$); meanwhile, CON exhibited sustained TSI% elevation throughout exercise above rest (Rest vs. 12th exercise minute: $62 \pm 5\%$ vs. $67 \pm 4\%$; $p < 0.05$). LC TSI% remained elevated above rest for a shorter duration of exercise compared to CON, worsening for LC on day 2. LC showed rapid normalization of TSI%, suggesting impaired muscle oxygenation and recovery during repeated exercise.»
Inclusion criteria: WHO definition (WHO, 2022)
- 49 ME/CFS and Long COVID Demonstrate Similar Bioenergetic Impairment and Recovery Failure on Two-Day Cardiopulmonary Exercise Testing**
Todd Davenport, Staci Stevens, Jared Stevens, Mark Van Ness
Clinical & Translational Metabolism, Version 1, Posted 22 Jan, 2026, Reviewers invited by journal 20 Jan, 2026, Editor assigned by journal 20 Jan, 2026, Submission checks completed at journal 18 Jan, 2026, First submitted to journal 14 Jan, 2026
<https://doi.org/10.21203/rs.3.rs-8606329/v1>
Conclusion/Main finding: «There were significant reductions in oxygen consumption (VO_2) and workload at the ventilatory anaerobic threshold (VAT) in both patient groups compared to non-disabled controls, with larger effect sizes at VAT than at peak exertion. Performance decrements were observed in both sexes. Females exhibited more pronounced abnormalities and significant group by test effects. No significant differences were observed between patient groups. Severe disability based on impaired VO_2 was prevalent in both patient groups. Hemodynamic and ventilatory measures were within normal ranges. ME/CFS and Long Covid both involve a functionally significant bioenergetic failure complicated by inadequate post-exertional recovery, which is similar between the conditions and unexplained by hemodynamic and ventilatory changes. Findings support the utility of two-day CPET as an objective measure of PEM and functional impairment.»
Inclusion criteria: unknown
- 48 Temporal dynamics of the plasma proteomic landscape reveals maladaptation in ME/CFS following exertion**
Arnaud Germain, Katherine A. Glass, Melissa A. Eckert, Ludovic Giloteaux, Maureen R. Hanson
Received November 4, 2024; Revised October 4, 2025; Accepted November 10, 2025; Published online November 11, 2025. DOI: 10.1016/j.mcpro.2025.101467. Also available on ScienceDirect. Copyright: © 2025 THE AUTHORS. Published by Elsevier Inc on behalf of American Society for Biochemistry and Molecular Biology.
[https://www.mcponline.org/article/S1535-9476\(25\)00566-3/fulltext](https://www.mcponline.org/article/S1535-9476(25)00566-3/fulltext)
Conclusion/Main finding: «Key findings included suppression of T and B cell signaling, downregulation of IL-17 and cell-cell communication pathways, and upregulation of glycolysis/gluconeogenesis, suggestive of mitochondrial stress and impaired immune recovery from exercise. Proteomic associations with physiological performance (VO_{2max} , anaerobic threshold) revealed disruptions between protein abundance and exercise capacity in ME/CFS versus controls. Correlations with symptom severity linked changes in immune-related proteins and ME/CFS symptoms including muscle pain, recurrent sore throat, and lymph node tenderness. Sex-stratified analyses revealed distinct molecular responses between females and

males, emphasizing the importance of considering sex as a biological variable in ME/CFS research. Finally, our analysis of sedentary controls contributes new data of molecular responses to acute exertion in a predominantly female sedentary cohort, a population historically underrepresented in exercise physiology studies. Together, these findings underscore the value of dynamic, proteomic profiling over time for characterizing maladaptive responses to exertion in ME/CFS and provide a foundation for deeper mechanistic investigation into PEM.»

Inclusion criteria: [Canada Consensus Criteria](#)



47 **Blood Flow to the Head in a Person With Myalgic Encephalomyelitis Experiencing Postexertional Malaise: A Case Report**

Christian, Caroline PhD; Lee, Daniel BSc; Stevens, Staci R. MA; Davenport, Todd E. PT, DPT, PhD, MPH, FAPTA; Stevens, Jared MPH; Dowell, Theresa PT, DNP; Van Ness, Mark PhD
 Cardiopulmonary Physical Therapy Journal ():10.1097/CPT.000000000000308, October 29, 2025. | DOI: 10.1097/CPT.000000000000308

https://journals.lww.com/acsm-msse/fulltext/2024/10001/blood_flow_to_the_head_is_reduced_in_a_patient.2013.aspx

Conclusion/Main finding: «Reduced blood flow to the head during PEM may partially explain ME symptomatology. The novel in-ear device shows promise as a diagnostic and biofeedback tool, warranting further research in larger studies.»

Inclusion criteria: with PEM

46 **Exercise-induced Changes in Microclotting and Cytokine Levels Point to Vascular Injury and Inflammation in People with Long COVID**

Callum Thomas, Massimo Nunes, Jan H. Pretorius, Ruth EM. Ashton, Isaac T. Shawa, Tom Bewick, Ethersia Pretorius, Douglas B. Kell, Mark A. Faghy
 Research square Version 1, posted 26 May, 2025
<https://doi.org/10.21203/rs.3.rs-6717727/v1>

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Conclusion/Main finding: « This study provides the first evidence of a biological basis that might explain exercise-induced symptom exacerbation in people with Long COVID through microclot fragmentation, which may contribute to systemic inflammation. This has important implications for Long COVID rehabilitation practices that seek to improve health outcomes through exercise therapies that may have the capacity to be harmful for people living with Long COVID and underscores the need for targeted therapeutic strategies that consider microclot clearance and endothelial repair.»

Inclusion criteria: [N/A, Long COVID](#)

45 **Towards an understanding of physical activity-induced post-exertional malaise: Insights into microvascular alterations and immunometabolic interactions in post-COVID condition and**

myalgic encephalomyelitis/chronic fatigue syndrome.

Simon Haunhorst, Diana Dudziak, Carmen Scheibenbogen, Martina Seifert, Franziska Sotzny, Carsten Finke, Uta Behrends, Konrad Aden, Stefan Schreiber, Dirk Brockmann, Paul Burggraf, Wilhelm Bloch, Claudia Ellert, Anuradha Ramoji, Juergen Popp, Philipp Reuken, Martin Walter, Andreas Stallmach and Christian Puta
Infection (2024). <https://doi.org/10.1007/s15010-024-02386-8>

Received 12 August 2024, Accepted 28 August 2024, Published 06 September 2024

<https://link.springer.com/article/10.1007/s15010-024-02386-8>

Conclusion/Main finding: «Upon physical activity, affected patients exhibit a reduced systemic oxygen extraction and oxidative phosphorylation capacity. Accumulating evidence suggests that these are mediated by dysfunctions in mitochondrial capacities and microcirculation that are maintained by latent immune activation, conjointly impairing peripheral bioenergetics. Aggravating deficits in tissue perfusion and oxygen utilization during activities cause exertional intolerance that are frequently accompanied by tachycardia, dyspnea, early cessation of activity and elicit downstream metabolic effects. The accumulation of molecules such as lactate, reactive oxygen species or prostaglandins might trigger local and systemic immune activation. Subsequent intensification of bioenergetic inflexibilities, muscular ionic disturbances and modulation of central nervous system functions can lead to an exacerbation of existing pathologies and symptoms.»

Inclusion criteria: [N/A, litteratur review](#)

44 Cardiopulmonary and metabolic responses during a 2-day CPET in myalgic encephalomyelitis/chronic fatigue syndrome: translating reduced oxygen consumption to impairment status to treatment considerations

Betsy Keller, Candace N. Receno, Carl J. Franconi, Sebastian Harenberg, Jared Stevens, Xiangling Mao, Staci R. Stevens, Geoff Moore, Susan Levine, John Chia, Dikoma Shungu and Maureen R. Hanson

Journal of Translational Medicine volume 22, Article number: 627 (2024)

<https://translational-medicine.biomedcentral.com/articles/10.1186/s12967-024-05410-5>

Conclusion/Main finding: « Unlike CTL, ME/CFS failed to reproduce CPET-1 measures during CPET-2 with significant declines at peak exertion in work, exercise time, \dot{V}_{O_2} , \dot{V}_{CO_2} , T, HR, \dot{V}_{O_2} pulse, DBP, and RPP. Likewise, CPET-2 declines were observed at VAT for \dot{V}_{CO_2} , PetCO₂, \dot{V}_{O_2} pulse, work, \dot{V}_{O_2} and SBP. Perception of effort (RPE) exceeded maximum effort criteria for ME/CFS and CTL on both CPETs. Results were similar in matched pairs. Intraclass correlations revealed greater stability in CPET variables across test days in CTL compared to ME/CFS owing to CPET-2 declines in ME/CFS. Lastly, CPET-2 data signaled more severe impairment status for ME/CFS compared to CPET-1.

Presently, this is the largest 2-d CPET study of ME/CFS to substantiate impaired recovery in ME/CFS following an exertional stressor. Abnormal post-exertional CPET responses persisted compared to CTL matched for aerobic capacity, indicating that fitness level does not predispose to exertion intolerance in ME/CFS. Moreover, contributions to exertion intolerance in ME/CFS by disrupted cardiac, pulmonary, and metabolic factors implicates autonomic nervous system dysregulation of blood flow and oxygen delivery for energy metabolism. The observable declines in post-exertional energy metabolism translate notably to a worsening of impairment status. Treatment considerations to address tangible reductions in physiological function are proffered.»

Inclusion criteria: [Canada Consensus Criteria](#)

43 Single-cell transcriptomics of the immune system in ME/CFS at baseline and following symptom provocation

Luyen Tien Vu, Faraz Ahmed, Hongya Zhu, David Shing Huk lu, Elizabeth A. Fogarty, Yeonui Kwak, Weizhong Chen, Carl J. Franconi, Paul R. Munn, Ann E. Tate, Susan M. Levine, Jared Stevens, Xiangling Mao, Dikoma C. Shungu, Geoffrey E. Moore, Betsy A. Keller, Maureen R. Hanson, Jennifer K. Grenier, Andrew Grimson

Cell Reports Medicine VOLUME 5, ISSUE 1, 101373, JANUARY 16, 2024

[https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791\(23\)00602-X](https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(23)00602-X)

Conclusion/Main finding: «Comparing the transcriptome at baseline and postexercise challenge, we discover patterns indicative of improper platelet activation in patients, with minimal changes elsewhere in the immune system. Taken together, these data identify immunological defects present at baseline in patients and an additional layer of dysregulation in platelets.»

Inclusion criteria: Unknown, but PEM are mentioned as mandatory. IOM-report 2015 is referred

42 A Unique Circular RNA Expression Pattern in the Peripheral Blood of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Patients

Yuning Cheng, Si-Mei Xu, Konii Takenaka, Grace Lindner, Ashton Curry-Hyde, Michael Janitz Gene, 2023, 147568, ISSN 0378-1119, <https://doi.org/10.1016/j.gene.2023.147568>.

<https://www.sciencedirect.com/science/article/pii/S0378111923004092>

Conclusion/Main finding: «This report comprises the first study on circRNA profile in ME/CFS. Here, expression profiling of circRNAs in ME/CFS patients and healthy individuals who underwent two CPETs over a seven-day period was analysed. We identified specific circRNAs showing differential expression at different time points, before and after exercise, as well as enriched GO terms implicated by the host genes of uniquely expressed circRNAs in ME/CFS patients.»

Inclusion criteria: [Ukjent, Fukuda et al., 1994, Carruthers et al., 2011](#) are mentioned

41 Exercise Pathophysiology in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Post-Acute Sequelae of SARS-CoV-2: More in Common Than Not?

Phillip Joseph, Inderjit Singh, Rudolf Oliveira, Christine A. Capone, Mary P. Mullen, Dane B. Cook, Mary Catherine Stovall, Johanna Squires, Kristine Madsen, Aaron B. Waxman, David M. Systrom, MD

To appear in: CHEST 5617, S0012-3692(23)00502-0, DOI: 10.1016/j.chest.2023.03.049

Received: 28 October 2022, Revised: 29 March 2023, Accepted: 30 March 2023, Published: April 11, 2023

[https://journal.chestnet.org/article/S0012-3692\(23\)00502-0/fulltext](https://journal.chestnet.org/article/S0012-3692(23)00502-0/fulltext)

Conclusion/Main finding: «PASC and ME/CFS overlap in both symptom burden and exercise derangements. Noninvasive CPET is useful in characterizing aerobic capacity and evaluating ventilatory inefficiency, the latter caused by hyperventilation. Two-day noninvasive CPET protocols may provide a diagnostic tool by showing a decrement in peak VO₂ on day two, potentially due to PEM. Neurovascular dysregulation observed with invasive CPET further explains exercise intolerance in PASC and ME/CFS through impaired cardiac preload and peripheral oxygen extraction, associated with autonomic dysfunction, small fiber neuropathy, ganglionopathy, and mitochondrial dysfunction. Future studies targeting these pathways are needed to reduce the substantial global burden of PASC and ME/CFS.»

Inclusion criteria: [SEID](#)

40 Two symptoms can accurately identify post-exertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome

Davenport, Todd E., Chu, Lily, Stevens, Staci R., Stevens, Jared, Snell, Christopher R., Van Ness, J. Mark

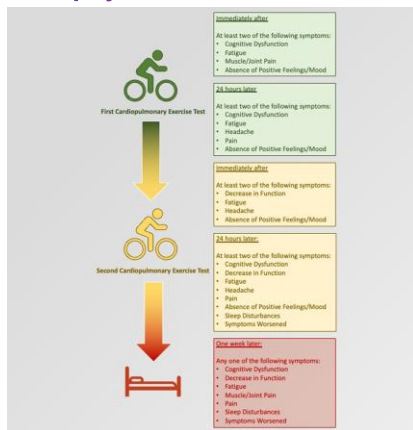
Journal: Work, vol. Pre-press, no. Pre-press, pp. 1-15, 2023. DOI: 10.3233/WOR-220554

Received 28 September 2022, Accepted 8 November 2022, Published: 13 March 2023

<https://content.iospress.com/articles/work/wor220554>

Conclusion/Main finding: «Although PEM is a complex phenomenon, researchers and clinicians may not have to engage in lengthy conversations or utilize complicated questionnaires to identify its existence. Medical professionals can efficiently assess for PEM by focusing on a specific set of post-exertional symptoms and the overall functional impact of those symptoms in the days following physical exertion.»

Inclusion criteria: Fukuda 1994 criteria (CDC) and self-reported PEM or had been diagnosed by their physician with ME/CFS.



39 Recovery from Exercise in Persons with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS).

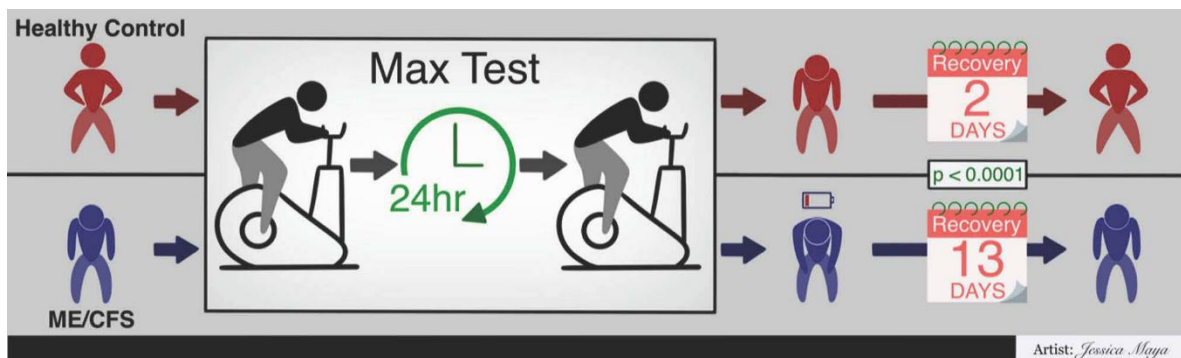
Moore GE, Keller BA, Stevens J, Mao X, Stevens SR, Chia JK, Levine SM, Franconi CJ, Hanson MR.

Medicina. 2023; 59(3):571. <https://doi.org/10.3390/medicina59030571>

<https://www.mdpi.com/1648-9144/59/3/571>

Conclusion/Main finding: «ME/CFS subjects took an average of about two weeks to recover from a 2-day CPET, whereas sedentary controls needed only two days. These data quantitate the prolonged recovery time in ME/CFS and improve the ability to obtain well-informed consent prior to doing exercise testing in persons with ME/CFS. Quantitative monitoring of PEM symptoms may provide a method to help manage PEM.»

Inclusion criteria: Canada Consensus Criteria



38 A 2-day cardiopulmonary exercise test in chronic fatigue syndrome patients who were exposed to humidifier disinfectants

Jong-Han Leem, Hyoung-Eun Jeon, Hun Nam, Hwan-Cheol Kim, Kyung-Lim Joa

Environmental Analysis Health and Toxicology Vol: 37(4), Article ID: e2022033, 7 pages

<https://doi.org/10.5620/eaht.2022033> eISSN: 2671-9525. Received: August 30, 2022 Accepted: October 19, 2022

<https://eaht.org/upload/pdf/eaht-37-4-e2022033.pdf>

Conclusion/Main finding: «In the 2-day CPET, the peak oxygen consumption (VO₂peak), VO₂ at ventilatory threshold (VO₂@VT), time to reach VO₂peak, and time to reach VO₂@VT were significantly decreased (p<0.001). The peak O₂ pulse and O₂ pulse at VT also decreased significantly (p<0.001). A 6-minute walk test revealed significantly decreased distance (p<0.01). ... Therefore, a 2-day CPET is an objective measure to differentiate fatigue conditions in people with CFS symptoms who have been exposed to HDs (humidifier disinfectants).»

Inclusion criteria: Fukuda/CDC

- 37 **Neurovascular Dysregulation and Acute Exercise Intolerance in ME/CFS: A Randomized, Placebo-Controlled Trial of Pyridostigmine**
Phillip Joseph, MD, Rosa Pari, MD, Sarah Miller, BS, Arabella Warren, BS, Mary Catherine Stovall, BS, Johanna Squires, MSc, Chia-Jung Chang, PhD, Wenzhong Xiao, PhD, Aaron B. Waxman, MD, PhD, David M. Systrom, MD
Accepted: April 22, 2022, Received in revised form: April 22, 2022, Received: February 27, 2022 Published: May 05, 2022 DOI: 10.1016/j.chest.2022.04.146
[https://journal.chestnet.org/article/S0012-3692\(22\)00890-X/pdf#relatedArticles](https://journal.chestnet.org/article/S0012-3692(22)00890-X/pdf#relatedArticles)
Conclusion/Main finding: «Pyridostigmine improves peak VO₂ in ME/CFS by increasing cardiac output and right ventricular filling pressures. Worsening peak exercise VO₂, Qc, and RAP after placebo may signal the onset of post-exertional malaise. We suggest treatable neurovascular dysregulation underlies acute exercise intolerance in ME/CFS.»
Inclusion criteria: [Unknown](#)
- 36 **Repeated maximal exercise tests of peak oxygen consumption in people with myalgic encephalomyelitis/chronic fatigue syndrome: a systematic review and meta-analysis**
John Derek Franklin & Michael Graham (2022)
Received 31 May 2022, Accepted 29 Jul 2022, Published online: 16 Aug 2022
Fatigue: Biomedicine, Health & Behavior, DOI: 10.1080/21641846.2022.2108628
<https://www.tandfonline.com/doi/full/10.1080/21641846.2022.2108628>
Conclusion/Main finding: «Synthesised data indicate that people with ME/CFS demonstrate a clinically significant test-retest reduction in work rate at the anaerobic threshold when compared to apparently healthy controls.»
Inclusion criteria: [Metaanalysis](#)
- 35 **Plasma metabolomics reveals disrupted response and recovery following maximal exercise in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome**
Arnaud Germain, Ludovic Giloteaux, Geoffrey E. Moore, Susan M. Levine, John K. Chia, Betsy A. Keller, Jared Stevens, Carl J. Franconi, Xiangling Mao, Dikoma C. Shungu, Andrew Grimson, and Maureen R. Hanson
Published March 31, 2022, JCI Insight. 2022. DOI: 10.1172/jci.insight.157621.
<https://insight.jci.org/articles/view/157621>
Conclusion/Main finding: «The 24-hour recovery period was distinct in the ME/CFS cohort, with over a quarter of the identified pathways statistically different. The pathways that are uniquely different 24 hours after an exercise challenge provide clues to metabolic disruptions that lead to PEM. Numerous altered pathways were observed to depend on glutamate metabolism, a crucial component to the homeostasis of many organs in the body, including the brain.»
Inclusion criteria: [Canada Consensus Criteria](#)
- 34 **Differential Effects of Exercise on fMRI of the Midbrain Ascending Arousal Network Nuclei in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Gulf War Illness (GWI) in a Model of Postexertional Malaise (PEM).**
Baraniuk JN, Amar A, Pepermitwala H, Washington SD.
Brain Sciences. 2022; 12(1):78. <https://doi.org/10.3390/brainsci12010078>
Received: 22 November 2021, Revised: 16 December 2021, Accepted: 21 December 2021, Published: 5 January 2022
Conclusion/Main finding: «Exercise caused the opposite effects with increased activation in ME/CFS but decreased activation in GWI, indicating different pathophysiological responses to exertion and mechanisms of disease. Midbrain and isthmus nuclei contribute to postexertional malaise in ME/CFS and GWI.»
Inclusion criteria: [Fukuda and Canadian criteria for ME/CFS](#)
- 33 **Review of the Midbrain Ascending Arousal Network Nuclei and Implications for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), Gulf War Illness (GWI) and Postexertional Malaise (PEM)**
James N. Baraniuk, Department of Medicine, Georgetown University, Washington, DC 20057,

USA

Academic Editor: Luigi De Gennaro

Brain Sci. 2022, 12(2), 132; DOI: 10.3390/brainsci12020132, Published: 19 January 2022

<https://www.mdpi.com/2076-3425/12/2/132/htm>

Conclusion/Main finding: «Prior to exercise, ME/CFS had generally lower blood oxygenation level dependent (BOLD) signals than controls. However, after exercise, ME/CFS had elevated activation of the anterior node of the DMN in the medial prefrontal cortex compared to pre-exercise and to controls»

Inclusion criteria: [Unknown, all though CDC, CCC, SEID and NICE-2020 draft guidelines are discussed](#)

- 32 Markers of Cardiac Autonomic Function During Consecutive Day Peak Exercise Tests in People With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome**
Maximillian J. Nelson¹, Jonathan D. Buckley, Rebecca L. Thomson, Clint R. Bellenger, Kade Davison
Front. Physiol., 14 December 2021 Sec. Exercise Physiology Volume 12 - 2021, DOI: 10.3389/fphys.2021.771899
<https://www.frontiersin.org/articles/10.3389/fphys.2021.771899/full>
Conclusion/Main finding: «Heart rate markers of autonomic function were unchanged in ME/CFS patients in the presence of post-exertional malaise, induced by maximal CPET on consecutive days. HR parameters assessed during this protocol are unlikely to represent a useful biomarker of the condition.»
Inclusion criteria: [1994 Centres For Disease Control and Prevention, 2003 'Canadian' Consensus Criteria or 2011 International Consensus Criteria.](#)
- 31 Submaximal Exercise Provokes Increased Activation of the Anterior Default Mode Network During the Resting State as a Biomarker of Postexertional Malaise in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome.**
Rayhan RU, Baraniuk JN.
Front Neurosci. 2021 Dec 15;15:748426. doi: 10.3389/fnins.2021.748426. PMID: 34975370; PMCID: PMC8714840.
<https://www.frontiersin.org/articles/10.3389/fnins.2021.748426/full>
Conclusion/Main finding: «The dynamic increase in activation of the anterior DMN node after exercise may be a biomarker of postexertional malaise and symptom exacerbation in CFS. The specificity of this postexertional finding in ME/CFS can now be assessed by comparison to post-COVID fatigue, Gulf War Illness, fibromyalgia, chronic idiopathic fatigue, and fatigue in systemic medical and psychiatric diseases.»
Inclusion criteria: [Fukuda/CDC and Canada Consensus Criteria](#)
- 30 The Prospects of the Two-Day Cardiopulmonary Exercise Test (CPET) in ME/CFS Patients: A Meta-Analysis.**
Lim EJ, Kang EB, Jang ES, Son CG.
J Clin Med. 2020 Dec 14;9(12):4040. doi: 10.3390/jcm9124040. PMID: 33327624; PMCID: PMC7765094.
<https://pubmed.ncbi.nlm.nih.gov/33327624/>
Conclusion/Main finding: «The overall mean values of all parameters were lower on the 2nd day of the CPET than the 1st in ME/CFS patients, while it increased in the controls. From the meta-analysis, the difference between patients and controls was highly significant at Workload@VT (overall mean: -10.8 at Test 1 vs. -33.0 at Test 2, $p < 0.05$), which may reflect present the functional impairment associated with PEM.»
Inclusion criteria: [Metaanalysis](#)
- 29 Comparing Idiopathic Chronic Fatigue and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) in Males: Response to Two-Day Cardiopulmonary Exercise Testing Protocol**
C. (Linda) M. C. van Campen and Frans C. Visser

Conclusion/Main finding: «This study confirms that male ME/CFS patients have a reduction in exercise capacity in response to a second-day CPET. These results are similar to published results in male ME/CFS populations. Patients diagnosed with ICF show a different response on day 2, more similar to sedentary and healthy controls».

Inclusion criteria: [International Consensus Criteria](#)

28 Deconditioning does not explain orthostatic intolerance in ME/CFS (myalgic encephalomyelitis/chronic fatigue syndrome)

van Campen, C.(Linda) M.C., Rowe, P.C. & Visser, F.C.

J Transl Med 19, 193 (2021). <https://doi.org/10.1186/s12967-021-02819-0>

https://translational-medicine.biomedcentral.com/articles/10.1186/s12967-021-02819-0?fbclid=IwAR3yCzJeDmmICIC0_GB-Aflja7d7YZqFWgaDljddZa5KM3_dD9S4O7kEfNc

Conclusion/Main finding: «This study shows that in ME/CFS patients orthostatic intolerance is not caused by deconditioning as defined on cardiopulmonary exercise testing. An abnormal high decline in cerebral blood flow during orthostatic stress was present in all ME/CFS patients regardless of their %peak VO₂ results on cardiopulmonary exercise testing».

Inclusion criteria: [Fukuda/CDC and International Consensus Criteria](#)

27 Insights From Invasive Cardiopulmonary Exercise Testing of Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (IKKE 2-DAGERS TEST!)

Phillip Joseph, MD, Carlo Arevalo, MD, Rudolf K.F. Oliveira, MD, PhD, Mariana Faria- Urbina, MD, Donna Felsenstein, MD, Anne Louise Oaklander, MD, PhD, David M. Systrom, MD

PII: S0012-3692(21)00256-7, DOI: <https://doi.org/10.1016/j.chest.2021.01.082>

Reference: CHEST 4020, To appear in: CHEST

Received Date: 22 September 2020, Revised Date: 22 January 2021, Accepted Date: 29 January 2021

[https://journal.chestnet.org/article/S0012-3692\(21\)00256-](https://journal.chestnet.org/article/S0012-3692(21)00256-7/abstract?fbclid=IwAR1PucGcap4HshTpnVwPJLExUS1R5oMaZA_IMuc1NY2Fcwoqh6dSdzhu)

[7/abstract?fbclid=IwAR1PucGcap4HshTpnVwPJLExUS1R5oMaZA_IMuc1NY2Fcwoqh6dSdzhu](https://journal.chestnet.org/article/S0012-3692(21)00256-7/abstract?fbclid=IwAR1PucGcap4HshTpnVwPJLExUS1R5oMaZA_IMuc1NY2Fcwoqh6dSdzhu)

[https://www.researchgate.net/profile/Rudolf-](https://www.researchgate.net/profile/Rudolf-Oliveira/publication/349183533_Insights_From_Invasive_Cardiopulmonary_Exercise_Testing_of_Patients_With_Myalgic_EncephalomyelitisChronic_Fatigue_Syndrome/links/6029dbb4a6fdc37a8290d7f/Insights-From-Invasive-Cardiopulmonary-Exercise-Testing-of-Patients-With-Myalgic-Encephalomyelitis-Chronic-Fatigue-Syndrome.pdf?origin=publication_detail)

[Oliveira/publication/349183533_Insights_From_Invasive_Cardiopulmonary_Exercise_Testing_of_Patients_With_Myalgic_EncephalomyelitisChronic_Fatigue_Syndrome/links/6029dbb4a6fdc37a8290d7f/Insights-From-Invasive-Cardiopulmonary-Exercise-Testing-of-Patients-With-Myalgic-Encephalomyelitis-Chronic-Fatigue-Syndrome.pdf?origin=publication_detail](https://www.researchgate.net/profile/Rudolf-Oliveira/publication/349183533_Insights_From_Invasive_Cardiopulmonary_Exercise_Testing_of_Patients_With_Myalgic_EncephalomyelitisChronic_Fatigue_Syndrome/links/6029dbb4a6fdc37a8290d7f/Insights-From-Invasive-Cardiopulmonary-Exercise-Testing-of-Patients-With-Myalgic-Encephalomyelitis-Chronic-Fatigue-Syndrome.pdf?origin=publication_detail)

Conclusion/Main finding: «These results identify two types of peripheral neurovascular dysregulation that are biologically plausible contributors to ME/CFS exertional intolerance—depressed Q_c [Cardiac output] from impaired venous return, and impaired peripheral oxygen extraction. In patients with small-fiber pathology, neuropathic dysregulation causing microvascular dilation may limit exertion by shunting oxygenated blood from capillary beds and reducing cardiac return».

Inclusion criteria: [SEID criteria \(acc. to IOM report 2015\)](#)

26 Exercise alters brain activation in Gulf War Illness and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Stuart D Washington, Rakib U Rayhan, Richard Garner, Destie Provenzano, Kristina Zajur, Florencia Martinez Addiego, John W VanMeter, James N Baraniuk,

Brain Communications, Volume 2, Issue 2, 2020, fcaa070, DOI: 10.1093/braincomms/fcaa070

<https://academic.oup.com/braincomms/article/2/2/fcaa070/5885074?login=false>

Conclusion/Main finding: «Further, exercise caused increased activation among Myalgic Encephalomyelitis/Chronic Fatigue Syndrome patients within the dorsal midbrain, left operculo-insular cortex (Rolandic operculum) and right middle insula. ... As they only emerge post-exercise, these regional differences likely represent neural substrates of cognitive post-

exertional malaise useful for developing distinct diagnostic criteria for Gulf War Illness and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome.»

Inclusion criteria: [Fukuda/CDC](#)

25 The Prospects of the Two-Day Cardiopulmonary Exercise Test (CPET) in ME/CFS Patients: A Meta-Analysis

Eun-Jin Lim, Eun-Bum Kang, Eun-Su Jang and Chang-Gue Son
J. Clin. Med. 2020, 9(12), 4040; DOI: 10.3390/jcm9124040

<https://www.mdpi.com/2077-0383/9/12/4040/htm?fbclid=IwAR3m3ac34cb1rVcJtcZkG6NIFLaMMc Bz rTCuX6shhVen47S>

[EG P ryPU](https://www.mdpi.com/2077-0383/9/12/4040/htm?fbclid=IwAR3m3ac34cb1rVcJtcZkG6NIFLaMMc Bz rTCuX6shhVen47S)

Conclusion/Main finding: *«The meta-analysis indicates a significant alteration of workload at VT especially on the 2nd day of CPET in ME/CFS patients. Accordingly, the two-day CPET could be considered as one of the potential objective assessment tools for PEM in ME/CFS patients.»*

Inclusion criteria: [Metaanalysis](#)

24 Post-exertional symptoms distinguish Myalgic Encephalomyelitis/Chronic Fatigue Syndrome subjects from healthy controls

Mateo, Lariel J.; Chu, Lily; Stevens, Staci; Stevens, Jared; Snell, Christopher R.; Davenport, Todd; VanNess, J. Mark

Journal: Work, vol. 66, no. 2, pp. 265-275, 2020, DOI: 10.3233/WOR-203168

<https://content.iospress.com/articles/work/wor203168>

Conclusion/Main finding: *«A standardized exertional stimulus produced prolonged, diverse symptoms in ME/CFS subjects. This provides clues to the underlying pathophysiology of ME/CFS, leading to improved diagnosis and treatment.»*

Inclusion criteria: [Fifteen of the 49 were formally recruited for the study and met the Fukuda \(1994\) criteria. The remaining 34 were physician diagnosed.](#)

23 Validity of 2-Day Cardiopulmonary Exercise Testing in Male Patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

van Campen, C. (Linda) M. C.; Rowe, Peter C.; Visser, Frans C. (2020).

Advances in Physical Education. 10 (01): 68-80. doi:10.4236/ape.2020.101007. ISSN 2164-0386.

<https://www.scirp.org/journal/paperinformation.aspx?paperid=98389>

Conclusion/Main finding: *«The larger sample size of this study improves the confidence with which we can conclude that, like females, males have a similar decrement on day 2 of the consecutive day exercise tests. Our results confirm that 2-day CPET can be used in males to demonstrate the decrease in exercise capacity in research studies and if needed for social security claims. Further comparisons are needed to explore whether the absolute or relative changes in VO₂ and workload on day 2 versus day 1 are similar across a wider range of clinical severity, and whether these values differ for subgroups with specific comorbid conditions.»*

Inclusion criteria: [Fukuda/CDC and International Consensus Criteria](#)

22 Two-Day Cardiopulmonary Exercise Testing in Females with a Severe Grade of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Comparison with Patients with Mild and Moderate Disease

C (Linda) MC van Campen, Peter C. Rowe, Frans C. Visser
Healthcare 2020, 8(3), 192; doi: 10.3390/healthcare8030192

<https://www.mdpi.com/2227-9032/8/3/192>

Conclusion/Main finding: *«This is the first study to demonstrate that disease severity negatively influences exercise capacity in female ME/CFS patients. Finally, this study shows that the deterioration in peak workload from day-1 to day-2 is largest in the severe ME/CFS patient group.»*

Inclusion criteria: [Fukuda/CDC and International Consensus Criteria](#)

21 Properties of measurements obtained during cardiopulmonary exercise testing in individuals with

myalgic encephalomyelitis/chronic fatigue syndrome.

Davenport TE, Stevens SR, Stevens MAJ, Snell CR, Van Ness

JM.Work. 2020 Jun 16. doi: 10.3233/WOR-203170. Online ahead of print.PMID: 32568145

<https://pubmed.ncbi.nlm.nih.gov/32568145/>

Conclusion/Main finding: «CPET measurements demonstrated moderate to high reliability for individuals with ME/CFS. Comparing subjects with ME/CFS and control subjects yielded moderate to large effect sizes on all CPET measurements. MDC95 for all individuals with ME/CFS generally exceeded control subjects and CoVs for CPET measurements were comparable between groups.»

Inclusion criteria: [Fukuda/CDC and International Consensus Criteria](#)

20 A Machine Learning Approach to the Differentiation of Functional Magnetic Resonance Imaging Data of Chronic Fatigue Syndrome (CFS) From a Sedentary Control

Destie Provenzano, Stuart D. Washington and James N. Baraniuk

Front. Comput. Neurosci., 29 January 2020 <https://doi.org/10.3389/fncom.2020.00002>

<https://www.frontiersin.org/articles/10.3389/fncom.2020.00002/full>

Conclusion/Main finding: «The logistic regression model performed on fMRI data significantly differentiated CFS from control with model accuracy of 80.9% on Day 1 before exercise and 76.1% on Day 2 during the period of post-exertional malaise.»

Inclusion criteria: [Fukuda/CDC, but argues for using Canada Consensus Criteria](#)

19 Elevated blood lactate in resting conditions correlate with post-exertional malaise severity in patients with Myalgic encephalomyelitis/Chronic fatigue syndrome

Alaa Ghali, Carole Lacout, Maria Ghali, Aline Gury, Anne-Berengere Beucher, Pierre Lozac'h, Christian Lavigne & Geoffrey Urbanski

Sci Rep. 2019 Dec 11;9(1):18817. doi: 10.1038/s41598-019-55473-4.

<https://www.nature.com/articles/s41598-019-55473-4?sfns=mo>

Conclusion/Main finding: «ME/CFS patients with elevated blood lactate at rest may be at higher risk for more severe PEM.»

Inclusion criteria: [International Consensus Criteria](#)

18 Unexplained exertional intolerance associated with impaired systemic oxygen extraction

Melamed KH, Santos M, Oliveira RKF, Urbina MF, Felsenstein D, Opatowsky AR, Waxman AB, Systrom DM.

Eur J Appl Physiol. 2019 Sep 6. doi: 10.1007/s00421-019-04222-6. PMID: 31493035.

<https://www.ncbi.nlm.nih.gov/pubmed/31493035>

Conclusion/Main finding: «We identified a cohort of patients whose exercise limitation is due only to systemic oxygen extraction, due to either an intrinsic abnormality of skeletal muscle mitochondrion, limb muscle microcirculatory dysregulation, or hyperventilation and left shift the oxyhemoglobin dissociation curve.»

About the study: <https://www.healthrising.org/blog/2019/12/11/oxygen-extraction-post-exertional-malaise-chronic-fatigue-syndrome/>

Inclusion criteria: [Own. Unexplained exertional intolerance, including those with suspected mitochondrial disease, were analyzed.](#)

17 Reproducibility of Measurements Obtained During Cardiopulmonary Exercise Testing in Individuals With Fatiguing Health Conditions - A Case Series

Larson B, Davenport TE, Stevens SR, Stevens J, Van Ness JM, Snell CR

Cardiopulmonary Physical Therapy Journal: June 24, 2019 - Volume Publish Ahead of Print - Issue - p

doi: 10.1097/CPT.000000000000100.

https://journals.lww.com/cptj/Abstract/2019/10000/Reproducibility_of_Measurements_Obtained_During.4.aspx

Conclusion/Main finding: «Nondisabled clients and clients with MS and HIV reproduced or improved in their volume of oxygen consumed (VO₂), workload (WL), heart rate (HR), and

minute ventilation (VE) at ventilatory anaerobic threshold (VAT) and at peak exercise (except peak WL and VE for the individual with HIV). Neither individual with ME/CFS reproduced VO₂, WL, HR, or VE at VAT within literature estimates.»

Inclusion criteria: [Canada Consensus Criteria](#)

- 16 Abnormal blood lactate accumulation during repeated exercise testing in myalgic encephalomyelitis/chronic fatigue syndrome.**
Lien K, Johansen B, Veierød MB, Haslestad AS, Bøhn SK, Melsom MN, Kardel KR, Iversen PO. *Physiol Rep.* 2019 Jun;7(11):e14138. doi: 10.14814/phy2.14138. PubMed PMID: 31161646; PubMed Central PMCID: PMC6546966. <https://www.ncbi.nlm.nih.gov/pubmed/31161646>
Conclusion/Main finding: *«In conclusion, previous exercise deteriorates physical performance and increases [Laa] during exercise in patients with ME/CFS while it lowers [Laa] in healthy subjects.»*
Inclusion criteria: [Canada Consensus Criteria](#)
- 15 Chronotropic Intolerance: An Overlooked Determinant of Symptoms and Activity Limitation in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome?**
Davenport TE, Lehnen M, Stevens SR, VanNess JM, Stevens J, Snell CR. *Front Pediatr.* 2019 Mar 22;7:82. doi: 10.3389/fped.2019.00082. eCollection 2019. Review. PubMed PMID: 30968005; PubMed Central PMCID: PMC6439478. <https://www.ncbi.nlm.nih.gov/pubmed/30968005>
Conclusion/Main finding: *«This literature synthesis supports the presence of abnormally blunted HR responses to activity in people with ME/CFS, at both maximal exertion and submaximal VAT.»*
Inclusion criteria: [Metaanalysis](#)
- 14 Whole blood human transcriptome and virome analysis of ME/CFS patients experiencing post-exertional malaise following cardiopulmonary exercise testing.**
Bouquet J, Li T, Gardy JL, Kang X, Stevens S, Stevens J, VanNess M, Snell C, Potts J, Miller RR, Morshed M, McCabe M, Parker S, Uyaguari M, Tang P, Steiner T, Chan WS, De Souza AM, Mattman A, Patrick DM, Chiu CY. *PLoS One.* 2019 Mar 21;14(3):e0212193. doi: 10.1371/journal.pone.0212193. eCollection 2019. PubMed PMID: 30897114; PubMed Central PMCID: PMC6428308. <https://www.ncbi.nlm.nih.gov/pubmed/30897114>
Conclusion/Main finding: *«Although ME/CFS patients showed significant worsening of symptoms following exercise versus controls, with 8 of 14 ME/CFS patients showing reduced oxygen consumption (VO₂) on day 2, transcriptome analysis yielded only 6 differentially expressed gene (DEG) candidates when comparing ME/CFS patients to controls across all time points.»*
Inclusion criteria: [Canada Consensus Criteria](#)
- 13 Diagnostic sensitivity of 2-day cardiopulmonary exercise testing in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome.**
Nelson MJ, Buckley JD, Thomson RL, Clark D, Kwiatek R, Davison K. *J Transl Med.* 2019 Mar 14;17(1):80. doi: 10.1186/s12967-019-1836-0. PubMed PMID: 30871578; PubMed Central PMCID: PMC6417168. <https://www.ncbi.nlm.nih.gov/pubmed/30871578>
Conclusion/Main finding: *«The decrease in WR (work rate) at VT (ventilatory threshold) of 6.3-9.8% on the 2nd day of consecutive-day CPET may represent an objective biomarker that can be used to assist with the diagnosis of ME/CFS.»*
Inclusion criteria: [Fukuda/CDC or Canada Consensus Criteria or International Consensus Criteria](#)
- 12 Cardiopulmonary Exercise Test Methodology for Assessing Exertion Intolerance in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome.**

Stevens S, Snell C, Stevens J, Keller B, VanNess JM.
Front Pediatr. 2018 Sep 4;6:242. doi: 10.3389/fped.2018.00242. eCollection 2018. PubMed
PMID: 30234078; PubMed Central PMCID: PMC6131594.
<https://www.ncbi.nlm.nih.gov/pubmed/30234078>

Conclusion/Main finding: «*The second CPET measures changes in energy production and physiological function, objectively documenting the effects of post-exertional malaise.*»

Inclusion criteria: [SEID criteria \(acc. to IOM report 2015\)](#) and [International Consensus Criteria](#)

- 11 **Physiological measures in participants with chronic fatigue syndrome, multiple sclerosis and healthy controls following repeated exercise: a pilot study.**
Hodges LD, Nielsen T, Baken D.
Clin Physiol Funct Imaging. 2018 Jul;38(4):639-644. doi: 10.1111/cpf.12460. Epub 2017 Aug 7.
PubMed PMID: 28782878. <https://www.ncbi.nlm.nih.gov/pubmed/28782878>
Conclusion/Main finding: «*These results suggest that exercise exhibits a different physiological response in MS and CFS/ME, demonstrating repeated cardiovascular exercise testing as a valid measure for differentiating between fatigue conditions.*»
Inclusion criteria: [Fukuda/CDC and Canada Consensus Criteria](#) and [International Consensus Criteria](#)

- 10 **A Pair of Identical Twins Discordant for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Differ in Physiological Parameters and Gut Microbiome Composition**
Giloteaux, Ludovic; Hanson, Maureen R.; Keller, Betsy A.
American Journal of Case Reports. 17: 720-729. doi:10.12659/AJCR.900314. ISSN 1941-5923.
PMC 5058431 Freely accessible. PMID 27721367. (Oct 10, 2016).
<https://www.amjcaserep.com/abstract/index/idArt/900314>
Conclusion/Main finding: «*Results suggest dysfunctional immune activation in ILL following exercise and that prokaryotic viruses may contribute to mucosal inflammation and bacterial dysbiosis. Therefore, a two-day CPET and molecular analyses of blood and microbiomes could provide valuable information about ME/CFS, particularly if applied to a larger cohort of monozygotic twins.*»
Inclusion criteria: [Unknown, but PEM is mentioned](#)

- 9 **Changes in Gut and Plasma Microbiome following Exercise Challenge in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS).**
Shukla SK, Cook D, Meyer J, Vernon SD, Le T, Clevidence D, Robertson CE, Schrodi SJ, Yale S, Frank DN.
PLoS One. 2015 Dec 18;10(12):e0145453. doi: 10.1371/journal.pone.0145453. eCollection 2015. PubMed PMID: 26683192; PubMed Central PMCID: PMC4684203.
<https://www.ncbi.nlm.nih.gov/pubmed/26683192>
Conclusion/Main finding: «*Upon exercise challenge, there were significant changes in the abundance of major bacterial phyla in the gut in ME/CFS patients not observed in healthy controls. In addition, compared to controls clearance of bacteria from the blood was delayed in ME/CFS patients following exercise.*»
Inclusion criteria: [Fukuda/CDC](#)

- 8 **Inability of myalgic encephalomyelitis/chronic fatigue syndrome patients to reproduce VO₂ peak indicates functional impairment.**
Keller BA, Pryor JL, Giloteaux L.
J Transl Med. 2014 Apr 23;12:104. doi: 10.1186/1479-5876-12-104. PubMed PMID: 24755065; PubMed Central PMCID: PMC4004422. <https://www.ncbi.nlm.nih.gov/pubmed/24755065>
Conclusion/Main finding: «*ME/CFS participants were unable to reproduce most physiological measures at both maximal and ventilatory threshold intensities during a CPET performed 24 hours after a prior maximal exercise test.*»
Inclusion criteria: [Fukuda/CDC](#)

- 7 Decreased oxygen extraction during cardiopulmonary exercise test in patients with chronic fatigue syndrome.**
 Vermeulen RC, Vermeulen van Eck IW.
 J Transl Med. 2014 Jan 23;12:20. doi: 10.1186/1479-5876-12-20. PubMed PMID: 24456560; PubMed Central PMCID: PMC3903040. <https://www.ncbi.nlm.nih.gov/pubmed/24456560>
 (Note! Ikke referert til i K Liens studie)
Conclusion/Main finding: «Low oxygen uptake by muscle cells causes exercise intolerance in a majority of CFS patients, indicating insufficient metabolic adaptation to incremental exercise. The high increase of the cardiac output relative to the increase of oxygen uptake argues against deconditioning as a cause for physical impairment in these patients.»
 Inclusion criteria: [Fukuda/CDC](#)
- 6 Discriminative validity of metabolic and workload measurements for identifying people with chronic fatigue syndrome.**
 Snell CR, Stevens SR, Davenport TE, Van Ness JM.
 Phys Ther. 2013 Nov;93(11):1484-92. doi: 10.2522/ptj.20110368. Epub 2013 Jun 27. PubMed PMID: 23813081. <https://www.ncbi.nlm.nih.gov/pubmed/23813081>
Conclusion/Main finding: «Multivariate analysis showed no significant differences between control participants and participants with CFS for test 1. However, for test 2, participants with CFS achieved significantly lower values for oxygen consumption and workload at peak exercise and at the ventilatory or anaerobic threshold. Follow-up classification analysis differentiated between groups with an overall accuracy of 95.1%.»
 Inclusion criteria: [Fukuda/CDC but PEM required](#)
- 5 Diagnostic accuracy of symptoms characterising chronic fatigue syndrome**
 Todd E. Davenport, Staci R. Stevens, Katie Baroni, Mark Van Ness & Christopher R. Snell (2011), Disability and Rehabilitation, 33:19-20, 1768-1775, DOI: 10.3109/09638288.2010.546936
<https://www.tandfonline.com/doi/abs/10.3109/09638288.2010.546936?journalCode=idre20>
Conclusion/Main finding: «A cluster of associated symptoms distinguishes between individuals with and without CFS. Fewer associated symptoms may be necessary to establish a diagnosis of CFS than currently described.»
 Inclusion criteria: [Fukuda/CDC](#)
- 4 Patients with chronic fatigue syndrome performed worse than controls in a controlled repeated exercise study despite a normal oxidative phosphorylation capacity.**
 Vermeulen RC, Kurk RM, Visser FC, Sluiter W, Scholte HR.
 J Transl Med. 2010 Oct 11;8:93. doi: 10.1186/1479-5876-8-93. PubMed PMID: 20937116; PubMed Central PMCID: PMC2964609. <https://www.ncbi.nlm.nih.gov/pubmed/20937116>
Conclusion/Main finding: «At both exercise tests the patients reached the anaerobic threshold and the maximal exercise at a much lower oxygen consumption than the controls and this worsened in the second test. This implies an increase of lactate, the product of anaerobic glycolysis, and a decrease of the mitochondrial ATP production in the patients.»
 Inclusion criteria: [Fukuda/CDC as consequence of infection](#)
- 3 Postexertional malaise in women with chronic fatigue syndrome.**
 VanNess JM, Stevens SR, Bateman L, Stiles TL, Snell CR.
 J Womens Health (Larchmt). 2010 Feb;19(2):239-44. doi: 10.1089/jwh.2009.1507. PubMed PMID: 20095909. <https://www.ncbi.nlm.nih.gov/pubmed/20095909>
Conclusion/Main finding: «The results of this study suggest that PEM is both a real and an incapacitating condition for women with CFS and that their responses to exercise are distinctively different from those of sedentary controls.»
 Inclusion criteria: [Fukuda/CDC](#)
- 2 Diminished Cardiopulmonary Capacity During Post-Exertional Malaise.**

Vanness, J. Mark; Snell, Christopher R.; Stevens, Staci R.
Journal of Chronic Fatigue Syndrome. 14 (2): 77-85. doi:10.1300/j092v14n02_07. ISSN 1057-3321. (Jan 2007).

https://www.tandfonline.com/doi/abs/10.1300/J092v14n02_07

Conclusion/Main finding: «*In the absence of a second exercise test, the lack of any significant differences for the first test would appear to suggest no functional impairment in CFS patients. However, the results from the second test indicate the presence of a CFS related post-exertional malaise. It might be concluded then that a single exercise test is insufficient to demonstrate functional impairment in CFS patients. A second test may be necessary to document the atypical recovery response and protracted malaise unique to CFS.*».

Inclusion criteria: [Fukuda/CDC](#)

1 Chronic fatigue syndrome: new evidence for a central fatigue disorder.

Georgiades E, Behan WM, Kilduff LP, Hadjicharalambous M, Mackie EE, Wilson J, Ward SA, Pitsiladis YP.

Clin Sci (Lond). 2003 Aug;105(2):213-8. doi: 10.1042/CS20020354. PubMed PMID: 12708966.

<https://www.ncbi.nlm.nih.gov/pubmed/12708966>

Conclusion/Main finding: «*the significant differences between patients with CFS and healthy controls that we observed in several key CNS 5-HT and dopaminergic modulators, assuming that they are indeed reflective of brain 5-HT and dopamine levels, suggest that central neural mechanisms may contribute to the increased perception of effort and impaired exercise tolerance in CFS.*»

Inclusion criteria: [Fukuda/CDC](#)