

# ME/CFS and Long COVID Exercise Research

A Systematic Analysis and Summary of 50 Studies  
on Post-Exertional Malaise and Cardiopulmonary Exercise Testing

Compiled and Analysed: April 26<sup>th</sup>, 2026

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## Executive Summary

This report synthesises the findings of 50 peer-reviewed studies (2003–2026) investigating exercise physiology, post-exertional malaise (PEM), and related biological mechanisms in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and, increasingly, Long COVID (Post-Acute Sequelae of SARS-CoV-2, PASC). The corpus spans more than two decades of research and includes cardiopulmonary exercise testing (CPET) studies, neuroimaging, metabolomics, proteomics, transcriptomics, microbiome research, and clinical trials.

Four overarching conclusions emerge across the evidence base:

- Two-day CPET is the most validated objective test for PEM and functional impairment in ME/CFS and Long COVID, consistently demonstrating a pathological decline in aerobic capacity on the second test day — a pattern not seen in healthy or sedentary controls.
- The underlying physiological defect centres on bioenergetic failure: impaired oxygen extraction, mitochondrial dysfunction, and microcirculatory dysregulation — not deconditioning or psychological factors.
- Multiple biological systems are dysregulated in response to exertion, including the immune system, autonomic nervous system, central nervous system, gut microbiome, blood coagulation, and metabolic pathways.
- ME/CFS and Long COVID share remarkably similar exercise-induced pathophysiology, lending support to common biological mechanisms across these conditions.

## Summary of Key Findings

Synthesised the 50 studies to the most critical points, we are left with the following conclusions:

1. **PEM is objectively measurable:** 2-day CPET tests show that patients' energy production fails fundamentally after the initial exertion. This distinguishes ME/CFS from deconditioning.
2. **Mitochondrial and vascular failure:** The body is unable to effectively transport oxygen from the blood into the muscle cells. This is likely due to a combination of mitochondrial dysfunction, microclots, and autonomic failure.
3. **Prolonged recovery time:** While healthy individuals recover within 48 hours, ME patients take an average of two weeks to return to baseline following maximal exertion (Study 39).
4. **Sex differences:** Females appear to have more pronounced abnormalities in physiological tests than males, although both sexes are significantly affected (Studies 49, 48).
5. **Exercise as medicine is risky:** Findings of vascular injury, inflammation, and metabolic collapse following exercise (46, 45) underscore why traditional exercise therapy often makes patients sicker.

**Conclusion:** ME/CFS and Long COVID are systemic, biological diseases characterized by a defective "energy motor." Research has moved away from psychological explanatory models and toward a detailed understanding of cellular and vascular dysfunction.

## Content

1. Overview of the Evidence Base — categorises all 49 studies by type (CPET studies, meta-analyses, neuroimaging, metabolomics, immunology, Long COVID, etc.) and notes the variation in diagnostic criteria used.
2. The Two-Day CPET: Core Evidence — the centrepiece of the report. Covers the physiological rationale, a table of all consistently declining parameters on Day 2, meta-analytic findings, sex and severity differences, recovery duration (~2 weeks vs ~2 days for controls), and discriminant validity against other fatiguing conditions.
3. Underlying Biological Mechanisms — eight subsections covering: bioenergetic/mitochondrial failure, neurovascular and autonomic dysregulation, CNS/brain involvement (fMRI), immune system dysregulation, metabolomics, gut microbiome, microclots in Long COVID, and circular RNA markers.
4. ME/CFS and Long COVID: Converging Evidence — synthesises studies #41, #45, #46, and #49 on the striking overlap in pathophysiology between the two conditions.
5. Clinical and Diagnostic Implications — covers two-day CPET as a diagnostic tool, impairment classification for disability contexts, symptom-based screening, and cautions regarding exercise therapy.
6. Study-by-Study Reference Table — a full table summarising all 49 studies by number, year/author, method, and primary finding.
7. Key Themes and Conclusions — addresses the deconditioning hypothesis (refuted), PEM as a measurable biological phenomenon, the ME/CFS–Long COVID convergence, and treatment implications.
8. Recommendations — separate evidence-based guidance for clinicians and researchers.
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## 1. Overview of the Evidence Base

The 50 studies reviewed span publication years from 2003 to early 2026. The majority were published between 2018 and 2026, reflecting a rapid acceleration in ME/CFS research following heightened awareness driven partly by the Long COVID pandemic. Below is a breakdown of the study types represented.

Study Type	Count	Key Examples (study numbers)
Two-day CPET (original research)	~22	#2, 3, 4, 6, 8, 11, 13, 16, 22, 23, 29, 32, 38, 39, 44, 49
Systematic reviews / meta-analyses	4	#25, 30, 36, 15
Neuroimaging / brain function	6	#1, 20, 26, 31, 33, 34
Metabolomics / proteomics	3	#35, 48, 42
Immunology / transcriptomics	3	#43, 14, 10
Invasive CPET / vascular	3	#27, 37, 18
Microbiome	2	#9, 10
Long COVID / PASC-focused	5	#41, 46, 49, 50, 45
Clinical / diagnostic tools	4	#5, 12, 21, 24, 40
Other (case reports, reviews)	3	#47, 28, 17

Diagnostic criteria used across studies vary, but most frequently employed are the Fukuda/CDC 1994 criteria, the Canadian Consensus Criteria (CCC), the International Consensus Criteria (ICC), and the SEID criteria from the 2015 IOM report. Studies using stricter criteria (CCC, ICC) tend to capture patients with more pronounced PEM, which may partly explain some variation in findings. Several recent Long COVID studies do not specify formal ME/CFS criteria, recruiting participants based on documented COVID-19 infection and persistent symptoms.

## 2. The Two-Day Cardiopulmonary Exercise Test (CPET): Core Evidence

### 2.1 Rationale and Background

Standard single-day maximal CPET in ME/CFS patients often produces results within normal or borderline ranges, failing to distinguish patients from healthy individuals (Study #2). The critical insight, first clearly documented in the early 2000s and now replicated many times, is that ME/CFS patients cannot reproduce their exercise performance 24 hours later, whereas healthy and sedentary controls either maintain or improve. This reproducibility failure is the physiological signature of PEM and forms the basis of the two-day CPET protocol.

### 2.2 Consistent Findings Across Studies

The following parameters show consistent, statistically significant decline on Day 2 in ME/CFS patients relative to controls:

Parameter	Direction in ME/CFS Day 2	Supporting Studies
Tissue Saturation Index (TSI%)	↓ Shorter elevation duration, worsens Day 2	#50
Peak VO <sub>2</sub> (oxygen consumption)	↓ Significant decline	#2, 3, 4, 6, 8, 13, 22, 23, 29, 38, 44, 49
VO <sub>2</sub> at ventilatory anaerobic threshold (VAT)	↓ More pronounced than peak	#6, 13, 25, 30, 36, 44, 49
Workload / work rate at VAT	↓ Most consistent finding	#4, 6, 13, 25, 30, 36, 44
O <sub>2</sub> pulse	↓ Decline	#44
Heart rate at VAT and peak	↓ Blunted response	#15, 32, 44
Exercise time	↓ Reduced	#44
Minute ventilation (VE)	↓ Decline	#44, 17
Systolic blood pressure	↓ At VAT	#44

### 2.3 Meta-Analytic Evidence

Four meta-analyses and systematic reviews (#15, #25, #30, #36) converge on the same conclusion. The 2020 meta-analysis (Study #25/#30, Lim et al.) found that workload at the ventilatory threshold was highly significantly altered, especially on Day 2, across all included ME/CFS populations. The 2022 systematic review and meta-analysis (Study #36, Franklin & Graham) specifically reported that people with ME/CFS show a clinically significant test-retest reduction in work rate at the anaerobic threshold compared to healthy controls. The chronotropic intolerance review (Study #15, Davenport et al.) further confirmed abnormally blunted heart rate responses to exercise at both maximal and submaximal levels.

## 2.4 Disease Severity and Sex Differences

Study #22 (van Campen et al., 2020) was the first to demonstrate that disease severity negatively influences exercise capacity, with the greatest Day 1 to Day 2 deterioration in peak workload observed in severely ill ME/CFS patients. Studies #22 and #23 established that the same Day 2 decline pattern holds across both sexes, though Study #49 (Davenport et al., 2026) found that females exhibit more pronounced abnormalities. The 2026 study also documented significant group-by-test interaction effects specifically in females, suggesting sex is an important biological variable.

## 2.5 Recovery Time

Study #39 (Moore et al., 2023) quantified recovery time after a two-day CPET: ME/CFS subjects required an average of approximately two weeks to recover, compared to only two days for sedentary controls. This dramatic difference in recovery kinetics provides critical context for understanding the disabling nature of PEM and the risks of exercise-based rehabilitation approaches.

## 2.6 Comparison with Other Fatiguing Conditions

A key strength of the two-day CPET literature is evidence of discriminant validity. Study #11 (Hodges et al.) showed that CFS and multiple sclerosis have distinct physiological responses to repeated exercise. Study #29 (van Campen & Visser, 2021) found that patients with idiopathic chronic fatigue (ICF) did NOT show the same Day 2 decline as ME/CFS patients — their response was more similar to sedentary controls. Study #17 (Larson et al.) confirmed that individuals with MS and HIV reproduced their CPET results, while neither ME/CFS individual did. This specificity supports the two-day CPET as a meaningful diagnostic discriminator.

## 3. Underlying Biological Mechanisms

### 3.1 Bioenergetic Failure and Mitochondrial Dysfunction

A central and recurring theme across the evidence base is impaired energy metabolism. Studies #4, #7, #16, #18, #44, and #45 all point to insufficient oxygen extraction and utilisation at the cellular level as the primary driver of exercise intolerance.

Study #4 (Vermeulen et al., 2010) demonstrated that ME/CFS patients reached both the anaerobic threshold and maximal exercise at much lower oxygen consumption than controls, with worsening on the second test, implying increased lactate production and decreased mitochondrial ATP production. Study #7 (Vermeulen & van Eck, 2014) showed that low oxygen uptake by muscle cells causes exercise intolerance in the majority of CFS patients, while the high increase in cardiac output relative to oxygen uptake argues against deconditioning as an explanation.

Study #16 (Lien et al., 2019) found abnormal blood lactate accumulation during repeated exercise in ME/CFS: prior exercise worsened physical performance and increased lactate levels in patients, while the opposite occurred in healthy subjects. Study #19 (Ghali et al., 2019) extended this by showing elevated resting blood lactate correlates with more severe PEM. Study #18 (Melamed et al., 2019) identified a cohort whose exercise limitation was attributable specifically to impaired systemic oxygen extraction, pointing to either intrinsic skeletal muscle mitochondrial abnormality or limb muscle microcirculatory dysregulation.

The 2024 narrative review (Study #45, Haunhorst et al.) synthesised this evidence, concluding that reduced systemic oxygen extraction and oxidative phosphorylation capacity are mediated by dysfunctions in mitochondrial capacities and microcirculation, maintained by latent immune activation, conjointly impairing peripheral bioenergetics.

### 3.2 Neurovascular Dysregulation and Autonomic Dysfunction

Autonomic nervous system dysregulation is a significant contributor to exercise intolerance in ME/CFS. Invasive CPET studies (#27, #37, #41) have been particularly illuminating.

Study #27 (Joseph et al., 2021) used invasive CPET with right heart catheterisation and identified two types of peripheral neurovascular dysregulation in ME/CFS: depressed cardiac output from impaired venous return, and impaired peripheral oxygen extraction. In patients with small-fibre neuropathy, neuropathic dysregulation causing microvascular dilation was proposed to limit exertion by shunting oxygenated blood away from capillary beds.

Study #37 (Joseph et al., 2022) conducted a randomised placebo-controlled trial of pyridostigmine (an acetylcholinesterase inhibitor) and found it improved peak VO<sub>2</sub> in ME/CFS by increasing cardiac output and right ventricular filling pressures. Worsening of these parameters after placebo was interpreted as signalling the onset of PEM, supporting treatable neurovascular dysregulation as a mechanism.

Study #28 (van Campen et al., 2021) addressed the deconditioning hypothesis directly, demonstrating that orthostatic intolerance in ME/CFS is not caused by deconditioning. All

ME/CFS patients showed an abnormally high decline in cerebral blood flow during orthostatic stress, regardless of their peak VO<sub>2</sub> results. Study #47 (Christian et al., 2025) extended this with a case report documenting reduced blood flow to the head during PEM using a novel in-ear device, suggesting this may partly explain ME/CFS symptomatology.

### 3.3 Central Nervous System Involvement

Six studies (#1, #20, #26, #31, #33, #34) used neuroimaging to investigate brain function in ME/CFS, particularly in response to exercise.

Study #1 (Georgiades et al., 2003) provided early evidence that central neural mechanisms — including serotonin and dopaminergic modulators — may contribute to increased perception of effort and impaired exercise tolerance. Studies #26, #31, #33, and #34 (Baraniuk and colleagues) used fMRI to map exercise-induced brain activation changes. Key findings include: prior to exercise, ME/CFS patients showed generally lower blood oxygenation level-dependent (BOLD) signals than controls; after exercise, ME/CFS showed elevated activation of the anterior default mode network (DMN) and dorsal midbrain — changes distinct from those seen in Gulf War Illness and not present in controls.

Study #31 (Rayhan & Baraniuk, 2021) proposed that the dynamic post-exercise increase in anterior DMN activation may serve as a biomarker of PEM in ME/CFS. Study #20 (Provenzano et al., 2020) demonstrated that a machine learning logistic regression model applied to fMRI data could differentiate CFS from controls with 80.9% accuracy before exercise and 76.1% accuracy during PEM, highlighting potential diagnostic utility of neuroimaging during PEM states.

### 3.4 Immune System Dysregulation

Multiple studies document abnormal immune responses to exertion. Study #43 (Vu et al., 2024) used single-cell transcriptomics at baseline and post-exercise, identifying patterns indicative of improper platelet activation in ME/CFS patients with minimal changes elsewhere in the immune system, alongside immunological defects present even at baseline.

Study #48 (Germain et al., 2025) applied longitudinal plasma proteomics following exercise challenge, finding suppression of T and B cell signalling, downregulation of IL-17 and cell-cell communication pathways, and upregulation of glycolysis/gluconeogenesis, suggestive of mitochondrial stress and impaired immune recovery. Sex-stratified analyses revealed distinct molecular responses between females and males.

Study #14 (Bouquet et al., 2019) conducted whole blood transcriptome analysis following CPET and found, although ME/CFS patients showed significant symptom worsening post-exercise, only 6 differentially expressed gene candidates were identified, suggesting that immune dysregulation in PEM may operate below conventional transcriptomic detection thresholds, or primarily through post-transcriptional mechanisms.

### 3.5 Metabolomics

Study #35 (Germain et al., 2022) applied plasma metabolomics before, immediately after, and 24 hours after maximal exercise. The 24-hour recovery period was distinct in ME/CFS, with over a quarter of identified pathways statistically different from controls. Glutamate metabolism was identified as a central disrupted pathway, with implications for multi-organ homeostasis including the brain. This study provides one of the most detailed windows into the metabolic cascade that underlies PEM.

### 3.6 Microbiome and Gut-Systemic Crosstalk

Two studies investigated the gut microbiome in the context of exercise challenge. Study #9 (Shukla et al., 2015) found significant changes in major gut bacterial phyla in ME/CFS patients following exercise not seen in healthy controls, and delayed clearance of bacteria from the blood in patients. Study #10 (Giloteaux et al., 2016), a twin discordant study, found dysfunctional immune activation in the ill twin following exercise and suggested prokaryotic viruses may contribute to mucosal inflammation and bacterial dysbiosis. Together, these studies raise the possibility that gut-immune axis disruption contributes to PEM.

### 3.7 Microclots and Vascular Injury in Long COVID

Study #46 (Thomas et al., 2025) provided the first evidence of a biological basis for exercise-induced symptom exacerbation in Long COVID via microclot fragmentation, contributing to systemic inflammation. This has direct implications for rehabilitation strategies and underscores the risk of exercise therapies that do not account for microclot clearance and endothelial repair. This finding resonates with the broader PEM literature across ME/CFS, where exercise is increasingly understood as potentially harmful rather than therapeutic.

### 3.8 Peripheral Muscle Oxygenation in Long COVID

Study #50 (Thomas et al., 2026) used near-infrared spectroscopy (NIRS) alongside two-day CPET to assess real-time peripheral tissue oxygenation in Long COVID. The tissue saturation index (TSI%) — a measure of local muscle oxygen availability — behaved abnormally in the Long COVID cohort compared to healthy controls. On Day 1, TSI% in Long COVID remained elevated above resting levels for only 2 minutes of exercise, compared to 5 minutes in controls, suggesting earlier exhaustion of local oxygen reserves. On Day 2, the Long COVID response worsened markedly: TSI% elevation above rest was confined to just the first exercise minute, while controls sustained elevation throughout 12 minutes of exercise. This rapid normalisation of TSI% in Long COVID indicates impaired muscle oxygenation and recovery capacity during repeated exertion — a peripheral oxygen delivery deficit that directly parallels the bioenergetic failure documented in ME/CFS. This study is among the first to capture the real-time muscular oxygenation dynamics underlying PEM-like responses in Long COVID, providing mechanistic detail that complements CPET measures.

### 3.9 Circular RNA and Genomic Markers

Study #42 (Cheng et al., 2023) conducted the first investigation of circular RNA (circRNA) profiles in ME/CFS, identifying specific circRNAs showing differential expression before and after exercise, with enriched gene ontology (GO) terms implicating the host genes of uniquely expressed circRNAs. This represents a nascent but potentially important avenue for biomarker discovery in ME/CFS.

## 4. ME/CFS and Long COVID: Converging Evidence

A significant development in the most recent literature (2022–2026) is the direct comparison of ME/CFS and Long COVID exercise pathophysiology. Studies #41, #45, #46, #49, and #50 all address this overlap.

Study #41 (Joseph et al., 2023) found that Long COVID (PASC) and ME/CFS overlap in both symptom burden and exercise derangements. Both conditions show impaired aerobic capacity, ventilatory inefficiency, and two-day CPET decrements potentially attributable to PEM. Neurovascular dysregulation — with impaired cardiac preload and peripheral oxygen extraction, autonomic dysfunction, small fibre neuropathy, ganglionopathy, and mitochondrial dysfunction — is identified as shared pathophysiology.

Study #49 (Davenport et al., 2026), a large two-day CPET study, found no significant differences in bioenergetic impairment between ME/CFS and Long COVID patient groups. Both showed significant reductions in VO<sub>2</sub> and workload at VAT compared to non-disabled controls, with larger effect sizes at VAT than at peak exertion, and both demonstrated inadequate post-exertional recovery unexplained by hemodynamic or ventilatory changes.

Study #50 (Thomas et al., 2026) extended this evidence to the peripheral muscle level, using near-infrared spectroscopy to demonstrate that Long COVID patients show impaired tissue oxygenation during exercise that worsens significantly on the second test day. The rapid normalisation of the tissue saturation index in Long COVID patients — in contrast to the sustained elevation seen in controls — provides direct evidence of impaired peripheral oxygen delivery, bridging the gap between the macroscopic CPET findings and the cellular bioenergetic mechanisms proposed across the broader literature.

Study #45 (Haunhorst et al., 2024) reviewed the mechanistic parallels, noting that both conditions involve reduced systemic oxygen extraction, microcirculatory dysfunction, mitochondrial impairment, and latent immune activation following physical activity.

These findings have important implications: they suggest that caution regarding exercise-based rehabilitation applies equally to Long COVID, and that insights from two decades of ME/CFS research may accelerate understanding and treatment of Long COVID.

## 5. Clinical and Diagnostic Implications

### 5.1 Two-Day CPET as an Objective Diagnostic Tool

The consistent reproducibility of Day 2 CPET declines across independent research groups, countries, and decades establishes the two-day CPET as a clinically valid objective measure of PEM and functional impairment. Study #6 (Snell et al., 2013) demonstrated classification accuracy of 95.1% in distinguishing ME/CFS from controls using Day 2 CPET data, compared to no significant group differences on Day 1. Study #13 (Nelson et al., 2019) identified a decrease in work rate at VT of 6.3–9.8% on Day 2 as a potential objective diagnostic biomarker.

Study #21 (Davenport et al., 2020) assessed measurement reliability, finding moderate to high reliability for CPET measurements in ME/CFS with moderate to large effect sizes when comparing ME/CFS to controls. Study #12 (Stevens et al., 2018) outlined CPET methodology specifically for assessing exertion intolerance in ME/CFS, confirming that the second CPET objectively documents the effects of PEM.

### 5.2 Impairment Classification and Disability Assessment

Study #44 (Keller et al., 2024), the largest two-day CPET study to date, found that CPET-2 data signals more severe impairment status for ME/CFS compared to CPET-1, with significant declines at peak exertion and at VAT. This worsening of impairment status has direct relevance for disability assessments and social security claims. Studies #22, #23, and #38 confirm the utility of two-day CPET across different patient subpopulations (female, male, exposed to environmental toxins).

### 5.3 Symptom-Based Diagnostic Approaches

Studies #5, #24, and #40 examined whether symptom assessment can serve as a complement or alternative to formal CPET. Study #40 (Davenport et al., 2023) found that two specific post-exertional symptoms and their functional impact could accurately identify PEM in ME/CFS patients, providing an efficient clinical tool for physicians. Study #24 (Mateo et al., 2020) showed that a standardised exertional stimulus produced prolonged, diverse post-exertional symptoms in ME/CFS subjects that clearly distinguished them from healthy controls.

### 5.4 Implications for Rehabilitation and Exercise Therapy

Taken collectively, the evidence in this corpus strongly cautions against graded exercise therapy (GET) as typically conceived for ME/CFS and Long COVID. The biological mechanisms identified — mitochondrial dysfunction, impaired peripheral oxygen delivery (Study #50), microvascular disruption, immune activation, microclot fragmentation, and abnormal lactate responses — suggest that increasing exercise load risks exacerbating disease pathology rather than improving it. Study #39 (Moore et al., 2023) emphasises that quantitative PEM monitoring may be necessary to safely manage any activity interventions. Study #44 explicitly offers treatment considerations addressing the tangible reductions in physiological function observed, advocating for approaches that target autonomic nervous system dysregulation and mitochondrial support.

## 6. Study-by-Study Reference Summary

The following table provides a condensed overview of all 49 studies by number, year, first author, methodology, and primary finding.

#	Year / Author(s)	Method	Primary Finding
1	2003 / Georgiades	Exercise + blood markers	Central neural mechanisms (serotonin/dopamine) contribute to increased effort perception and impaired exercise tolerance in CFS.
2	2007 / VanNess	2-day CPET	Single-day CPET insufficient to demonstrate CFS impairment; second test reveals pathological post-exertional malaise and recovery failure.
3	2010 / VanNess	2-day CPET (women)	PEM is real and incapacitating in women with CFS; exercise responses distinctively different from sedentary controls.
4	2010 / Vermeulen	2-day CPET + mitochondria	ME/CFS patients reached anaerobic threshold at much lower VO <sub>2</sub> ; worsened on Day 2, indicating increased lactate and reduced mitochondrial ATP.
5	2011 / Davenport	Symptom cluster analysis	A cluster of symptoms distinguishes CFS from non-CFS; fewer symptoms needed for diagnosis than previously described.
6	2013 / Snell	2-day CPET	Day 2 CPET classifies ME/CFS vs controls with 95.1% accuracy; no group differences on Day 1.
7	2014 / Vermeulen	CPET + oxygen extraction	Low oxygen uptake by muscle cells causes exercise intolerance; high cardiac output increase argues against deconditioning.
8	2014 / Keller	2-day CPET	ME/CFS patients unable to reproduce most physiological measures at maximal and VT intensities 24 hours after first CPET.
9	2015 / Shukla	Microbiome + CPET	Significant changes in gut bacterial phyla in ME/CFS post-exercise; delayed blood bacterial clearance in patients vs. controls.
10	2016 / Giloteaux	Twin study + CPET	Dysfunctional immune activation following exercise in the ill twin; potential contribution of prokaryotic viruses to mucosal inflammation.
11	2018 / Hodges	2-day CPET (comparative)	CFS and MS have distinct physiological responses to repeated exercise, supporting discriminant validity.
12	2018 / Stevens	CPET methodology review	Standardised methodology for two-day CPET in ME/CFS; second CPET objectively documents PEM effects.
13	2019 / Nelson	2-day CPET + sensitivity	Day 2 work rate decrease at VT of 6.3–9.8% represents a potential objective diagnostic biomarker for ME/CFS.
14	2019 / Bouquet	Transcriptomics + CPET	Significant symptom worsening post-exercise; only 6 differentially expressed genes identified — immune dysregulation may operate post-transcriptionally.
15	2019 / Davenport	Meta-analysis (HR)	Abnormally blunted heart rate responses to activity confirmed in ME/CFS at both maximal and submaximal exercise.
16	2019 / Lien	2-day CPET + lactate	Prior exercise worsens performance and increases blood lactate in ME/CFS; opposite effect in healthy

#	Year / Author(s)	Method	Primary Finding
			controls.
17	2019 / Larson	Case series CPET	Individuals with MS and HIV reproduce CPET results; neither ME/CFS patient reproduced VO <sub>2</sub> or workload at VAT.
18	2019 / Melamed	Invasive CPET	Exercise limitation in a subgroup attributable to impaired systemic oxygen extraction: mitochondrial or microvascular aetiology.
19	2019 / Ghali	Lactate at rest + PEM	Elevated resting blood lactate in ME/CFS correlates with more severe PEM.
20	2020 / Provenzano	fMRI + machine learning	Logistic regression on fMRI data differentiates CFS from controls at 80.9% (pre-exercise) and 76.1% (during PEM) accuracy.
21	2020 / Davenport	CPET reliability	Moderate-to-high reliability for CPET measurements in ME/CFS; moderate-to-large effect sizes vs. controls.
22	2020 / van Campen	2-day CPET (severe women)	First study showing disease severity negatively influences exercise capacity; greatest Day 2 deterioration in severe ME/CFS.
23	2020 / van Campen	2-day CPET (males)	Male ME/CFS patients show same Day 2 decline as females; two-day CPET valid for males in research and disability contexts.
24	2020 / Mateo	Symptom provocation	Standardised exertion produces prolonged, diverse symptoms in ME/CFS subjects, clearly distinguishing them from healthy controls.
25	2020 / Lim	Meta-analysis	Significant workload alteration at VT on Day 2; two-day CPET a potential objective PEM assessment tool.
26	2020 / Washington	fMRI + exercise	Post-exercise: ME/CFS shows increased activation in dorsal midbrain and insulae — neural substrates of cognitive PEM.
27	2021 / Joseph	Invasive CPET	Two types of peripheral neurovascular dysregulation identified: impaired venous return and impaired peripheral oxygen extraction.
28	2021 / van Campen	OI + CPET	Orthostatic intolerance in ME/CFS not caused by deconditioning; abnormal cerebral blood flow decline during orthostatic stress.
29	2021 / van Campen	2-day CPET (males, ICF)	ME/CFS males show Day 2 decline; idiopathic chronic fatigue patients respond like sedentary controls, confirming discriminant validity.
30	2020 / Lim	Meta-analysis	All CPET parameters lower on Day 2 in ME/CFS; controls improved. Workload at VT Day 2 highly significant vs. controls.
31	2021 / Rayhan	fMRI + submaximal exercise	Post-exercise increased anterior DMN activation proposed as biomarker of PEM in ME/CFS.
32	2021 / Nelson	Heart rate autonomic CPET	Heart rate autonomic markers unchanged during PEM induced by two-day CPET — HR parameters unlikely to be useful biomarkers alone.
33	2022 / Baraniuk	Midbrain review	Review implicates midbrain ascending arousal network nuclei in PEM pathophysiology for ME/CFS and Gulf War Illness.
34	2022 / Baraniuk	fMRI + exercise	Exercise caused increased midbrain activation in ME/CFS but decreased in GWI, indicating different disease mechanisms.

#	Year / Author(s)	Method	Primary Finding
35	2022 / Germain	Plasma metabolomics	24-hour recovery in ME/CFS showed >25% of metabolic pathways significantly different; glutamate metabolism central to PEM.
36	2022 / Franklin	Systematic review + meta	Clinically significant test-retest reduction in work rate at anaerobic threshold in ME/CFS vs. healthy controls.
37	2022 / Joseph	RCT: pyridostigmine	Pyridostigmine improved peak VO <sub>2</sub> in ME/CFS by increasing cardiac output and right ventricular filling; treatable neurovascular dysregulation confirmed.
38	2022 / Leem	2-day CPET (HDs exposure)	VO <sub>2</sub> peak, VO <sub>2</sub> @VT, and O <sub>2</sub> pulse significantly decreased on Day 2; two-day CPET differentiates CFS from other fatigue after toxic exposure.
39	2023 / Moore	Recovery duration post-CPET	ME/CFS requires ~2 weeks to recover from two-day CPET; sedentary controls recover in ~2 days.
40	2023 / Davenport	PEM identification	Two specific post-exertional symptoms and their functional impact can accurately identify PEM in ME/CFS.
41	2023 / Joseph	CPET: ME/CFS vs PASC	ME/CFS and Long COVID share symptom burden and exercise derangements; neurovascular dysregulation is common pathophysiology.
42	2023 / Cheng	Circular RNA + CPET	First circRNA profiling in ME/CFS; specific circRNAs differentially expressed before and after exercise.
43	2024 / Vu	scRNA-seq + CPET	Improper platelet activation post-exercise in ME/CFS; immunological defects at baseline; minimal immune changes elsewhere.
44	2024 / Keller	2-day CPET (largest study)	Largest 2-day CPET study: ME/CFS fails to reproduce CPET-1; autonomic, cardiac, and metabolic factors all impaired; Day 2 worsens impairment status.
45	2024 / Haunhorst	Narrative review	Physical activity in ME/CFS/Long COVID: reduced oxygen extraction and OXPHOS capacity from mitochondrial and microvascular dysfunction, maintained by immune activation.
46	2025 / Thomas	Microclots + Long COVID	First evidence of microclot fragmentation as biological basis for exercise-induced symptom exacerbation in Long COVID; caution re exercise therapies.
47	2025 / Christian	Blood flow case report	Reduced blood flow to the head during PEM; novel in-ear device shows promise as a diagnostic/biofeedback tool.
48	2025 / Germain	Plasma proteomics	Suppressed T/B cell signalling, downregulated IL-17, upregulated glycolysis post-exercise; mitochondrial stress and impaired immune recovery; sex-specific differences.
49	2026 / Davenport	2-day CPET: ME/CFS vs LC	No significant difference between ME/CFS and Long COVID on two-day CPET; both show bioenergetic failure and inadequate post-exertional recovery; larger effects at VAT than peak.
50	2026 / Thomas	2-day CPET + NIRS (Long COVID)	Impaired peripheral oxygen delivery in Long COVID on Day 2: tissue saturation index elevation shorter-lived and worsened on Day 2; rapid normalisation suggests impaired muscle oxygenation and recovery during repeated exercise.

## 7. Key Themes and Conclusions

### 7.1 The Deconditioning Hypothesis Is Unsupported

Multiple lines of evidence directly refute the hypothesis that ME/CFS exercise intolerance is caused by physical deconditioning. Studies #7, #28, and #44 each independently demonstrate this. Cardiac output in ME/CFS is often appropriate or elevated relative to oxygen consumption (Study #7); orthostatic intolerance is independent of fitness level (Study #28); and declines in post-exertional energy metabolism persist even when ME/CFS patients are matched to controls for aerobic capacity (Study #44).

### 7.2 PEM Is a Distinct, Measurable Biological Phenomenon

Across multiple biological levels — physiology, metabolism, immunology, neuroscience, genomics, and the microbiome — exertion produces measurably abnormal responses in ME/CFS that are not present in healthy, sedentary, or comparator disease populations. This evidence base establishes PEM as a genuine biological pathology, not a psychological phenomenon or exaggerated symptom perception.

### 7.3 Convergence Between ME/CFS and Long COVID

The most recent studies provide compelling evidence that ME/CFS and Long COVID share fundamental pathophysiological mechanisms. This convergence offers a historic opportunity: the unprecedented research investment triggered by the COVID-19 pandemic may accelerate understanding of ME/CFS, and conversely, two decades of ME/CFS research provides an evidence base for managing Long COVID that should not be ignored.

### 7.4 Treatment Implications

The evidence points towards several treatment targets: autonomic nervous system support (demonstrated by the pyridostigmine trial, Study #37); mitochondrial and metabolic support (consistent with bioenergetic failure findings across the corpus); microclot and endothelial repair strategies (Study #46); and pacing-based activity management informed by heart rate thresholds and PEM monitoring (Study #39). The literature consistently and strongly contraindicates graded exercise therapy that does not account for these biological realities.

### 7.5 Methodological Strengths and Limitations

The strongest studies in this corpus use the Canadian Consensus Criteria or International Consensus Criteria, ensuring that patients with definite PEM are included. Studies using only the Fukuda/CDC criteria (which do not require PEM) may inadvertently include heterogeneous fatigue populations, potentially attenuating effect sizes. Sample sizes across much of the CPET literature remain modest, though Study #44 represents significant progress with its larger cohort. The field would benefit from multi-site studies with pre-registered protocols, standardised diagnostic criteria, and longer follow-up to assess disease trajectory and treatment response.

## 8. Recommendations for Clinicians and Researchers

### For Clinicians

- Consider two-day CPET as the gold standard objective assessment for PEM and functional impairment in ME/CFS and Long COVID when clinical resources permit.
- Use the two-symptom screening tool (Study #40) for efficient PEM identification in clinical settings.
- Refrain from prescribing graded exercise therapy that increases exercise load without careful, individualised PEM monitoring.
- Screen for orthostatic intolerance, autonomic dysfunction, and cerebral blood flow abnormalities as part of ME/CFS/Long COVID workup.
- Recognise that disease severity significantly impacts exercise capacity (Study #22) and that recovery from exertion may take weeks (Study #39).

### For Researchers

- Prioritise the use of ME/CFS diagnostic criteria that require PEM (CCC, ICC) to ensure homogeneous study populations.
- Incorporate sex-stratified analyses as standard, given consistent evidence of differential responses in females and males (Studies #49, #48, #22).
- Continue longitudinal multi-omics studies combining metabolomics, proteomics, transcriptomics, and microbiome analysis in response to standardised exercise challenge.
- Invest in biomarker development — particularly plasma proteomic, metabolomic, and neuroimaging signatures of PEM — to enable diagnosis without requiring the clinical risk of exercise testing.
- Pursue mechanistic trials targeting neurovascular dysregulation, mitochondrial function, and microclot/endothelial pathology.
- Expand Long COVID/ME/CFS comparative studies to build on the strong preliminary convergence evidence from Studies #41, #45, and #49.

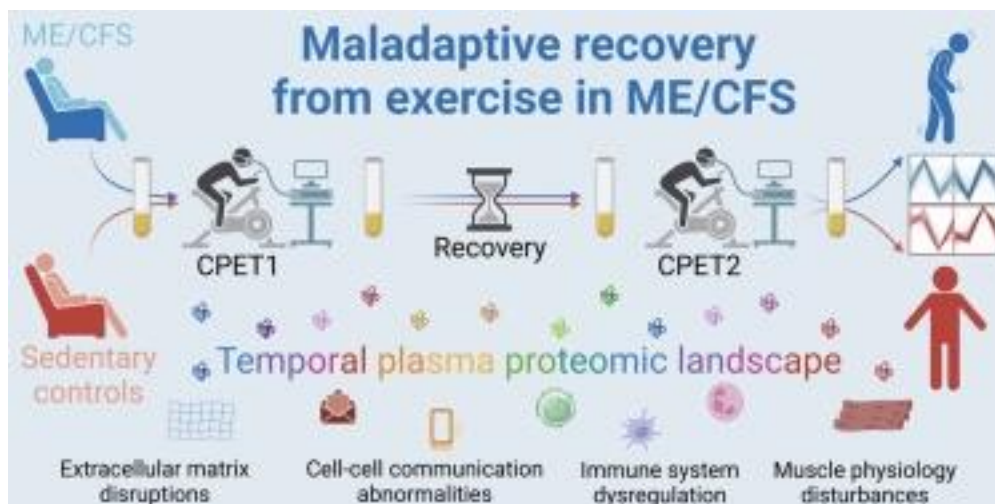
— End of Report —

## References

- 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<sub>2</sub>max, 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](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  $\dot{V}_{CO_2}$ , PetCO<sub>2</sub>,  $\dot{V}_{O_2}$ 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 Iu, 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 VO<sub>2</sub> 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

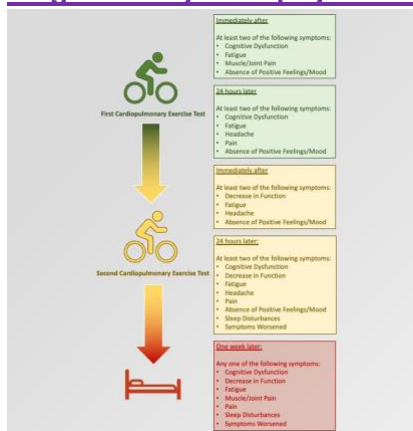
Journal: Work, vol. Pre-press, no. Pre-press, pp. 1-15, 2023. DOI: 10.3233/WOR-220554

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).**

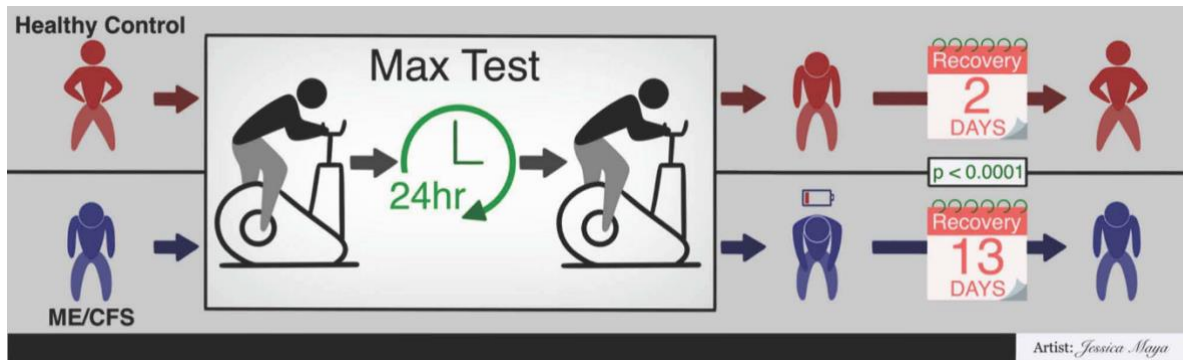
Moore GE, Keller BA, Stevens J, Mao X, Stevens SR, Chia JK, Levine SM, Franconi CJ, Hanson MR.

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, Hyung-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 ( $VO_{2peak}$ ),  $VO_2$  at ventilatory threshold ( $VO_{2@VT}$ ), time to reach  $VO_{2peak}$ , and time to reach  $VO_{2@VT}$  were significantly decreased ( $p < 0.001$ ). The peak  $O_2$  pulse and  $O_2$  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  $VO_2$  in ME/CFS by increasing cardiac output and right ventricular filling pressures. Worsening peak exercise  $VO_2$ ,  $Q_c$ , 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. Nelson<sup>1</sup>, 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

Healthcare 2021, 9(6), 683; <https://doi.org/10.3390/healthcare9060683> (registering DOI)

Received: 22 April 2021 / Revised: 3 June 2021 / Accepted: 3 June 2021 / Published: 5 June 2021

<https://www.mdpi.com/2227-9032/9/6/683>

**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](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 VO<sub>2</sub> 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_IMuc1NY2Fcwogh6dSdzhu)

[7/abstract?fbclid=IwAR1PucGcap4HshTpnVwPJLExUS1R5oMaZA\\_IMuc1NY2Fcwogh6dSdzhu](https://journal.chestnet.org/article/S0012-3692(21)00256-7/abstract?fbclid=IwAR1PucGcap4HshTpnVwPJLExUS1R5oMaZA_IMuc1NY2Fcwogh6dSdzhu)

[Tol](https://journal.chestnet.org/article/S0012-3692(21)00256-7/abstract?fbclid=IwAR1PucGcap4HshTpnVwPJLExUS1R5oMaZA_IMuc1NY2Fcwogh6dSdzhu)

[https://www.researchgate.net/profile/Rudolf-Oliveira/publication/349183533\\_Insights\\_From\\_Invasive\\_Cardiopulmonary\\_Exercise\\_Testing\\_of\\_Patients\\_With\\_Myalgic\\_EncephalomyelitisChronic\\_Fatigue\\_Syndrome/links/6029dbb4a6fdcc37a8290d7f/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/6029dbb4a6fdcc37a8290d7f/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<sub>c</sub> [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=IwAR3m3ac34cbl1rVcJtcZkG6NIFLaMMc\\_Bz\\_rTCuX6shhVen47SEGP\\_ryPU](https://www.mdpi.com/2077-0383/9/12/4040/htm?fbclid=IwAR3m3ac34cbl1rVcJtcZkG6NIFLaMMc_Bz_rTCuX6shhVen47SEGP_ryPU)

[https://www.mdpi.com/2077-0383/9/12/4040/htm?fbclid=IwAR3m3ac34cbl1rVcJtcZkG6NIFLaMMc\\_Bz\\_rTCuX6shhVen47SEGP\\_ryPU](https://www.mdpi.com/2077-0383/9/12/4040/htm?fbclid=IwAR3m3ac34cbl1rVcJtcZkG6NIFLaMMc_Bz_rTCuX6shhVen47SEGP_ryPU)

**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 VO<sub>2</sub> 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](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 (VO<sub>2</sub>), 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 VO<sub>2</sub>, 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 (VO<sub>2</sub>) 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 VO<sub>2</sub>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](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**