

Stage 1- Does poor oxygenation and a delay in muscle energy recovery contribute to fatigue and PEM in ME/CFS?

Grant Amount	£39,554.13 (for Stage 1)
Location	Oxford Centre for Clinical Magnetic Resonance Research (OCMR), University of Oxford
Research Field	Biological causes and Biomarker discovery
Lead Researcher/s	Professor Ladislav Valkovič
Start Date	01/04/2026
Duration	12 months
Status	In progress
Latest Update	Research Update: Understanding Muscle Energy Production and Oxygen Use During PEM in ME/CFS

BACKGROUND

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a complex, debilitating condition characterised by overwhelming fatigue and post-exertional malaise (PEM) — the worsening of symptoms after even minor physical or mental activity. PEM is central to the illness, yet its biological basis remains poorly understood.

Mitochondria generate over 90% of the body's cellular energy, and when they fail to meet demand, fatigue and metabolic dysfunction can occur. ME/CFS research has long suggested abnormalities in these energy-production pathways, particularly during exertion. However, traditional methods for studying muscle metabolism often rely on invasive biopsies or isolated cell studies, which are not ideal for patients and limit large-scale investigation.

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Understanding changes in muscle energy production and oxygenation during PEM by utilization of two state-of-the-art in-vivo measurement techniques

This project offers a non-invasive, patient-friendly approach using two advanced techniques:

- **Magnetic Resonance Imaging (MRI)** to measure phosphocreatine (PCr) recovery, providing direct insight into mitochondrial energy production.

"PCr recovery gives direct and non-invasive insight into oxidative energy production."

- **Near-Infrared Spectroscopy (NIRS)** to assess muscle oxygenation and blood-flow dynamics using a small light probe on the skin.

"This rapid… assessment of muscle oxygenation… involves a small light probe on the skin."

Together, these methods allow researchers to investigate mitochondrial function in vivo, without biopsies, and to explore how energy metabolism changes during PEM.

PROJECT DETAILS

This two-stage case-control study will examine mitochondrial function in the calf muscle of people with mild ME/CFS and sedentary healthy controls. The project is hosted at the Oxford Centre for Clinical Magnetic Resonance Research (OCMR) and supported by the Centre for Movement, Occupation and Rehabilitation Sciences at Oxford Brookes University.

Project aims:

Across two stages, the research team will examine:

- **Baseline mitochondrial function** in people with mild ME/CFS compared with sedentary healthy controls.
- **Changes in mitochondrial function during PEM**, using repeated MRI and NIRS assessments.
- Whether impaired energy recovery and reduced oxygen utilisation help explain PEM.
- Whether NIRS can be validated as a **portable, scalable diagnostic tool** for clinical practice.

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The team hypothesise that:

- People with ME/CFS will show **decreased mitochondrial function** at rest.
- During PEM, MRI and NIRS will reveal **much slower energy recovery**, indicating exercise-inflated mitochondrial dysfunction.

"Repeated MRI and NIRS experiments while the patients will be in PEM will show even slower energy recovery… suggesting exercise-inflated mitochondrial dysfunction as a contributor to PEM."

STUDY DESIGN

Stage 1 Baseline Cross-Sectional Study (01 April 2026 – 31 March 2027):

Aim: To understand how muscle energy production and recovery in people with ME/CFS differs from healthy individuals during mild exercises completed while being scanned.

Participants: 20 people with mild ME/CFS and 10 sedentary healthy controls.

What happens in Phase 1: All participants attend one research visit (healthy controls attend two). During the visit they will:

- Provide a blood sample
- Provide a urine sample
- Complete symptom and wellbeing questionnaires
- Undergo MRI testing involving light plantar-flexion exercise followed by recovery
- Complete a NIRS assessment involving heel-raises and brief blood-flow restriction
- Wear a smartwatch for several days to monitor activity patterns

MRI will measure how quickly the muscle replenishes phosphocreatine after exercise, while NIRS will assess oxygen utilisation and recovery.

Healthy controls will also undergo sub-maximal exercise testing on a stationary bike and be asked to return for a second visit several days later, to repeat the exercise and the to assess any variations.

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Why Stage 1 matters: This stage establishes a baseline and helps determine if people with ME/CFS might have problems in muscle energy production and recovery. It also validates MRI and NIRS as complementary tools before moving into Stage 2 with its focus on post-exertional malaise (PEM).

N.B. Stage 1 ethical approval has been granted by the University (Ref: MS IDREC 1410399), study name Muscle Energy in ME/CFS (MEiME).

Stage 2 Mitochondrial Function During PEM (Funding Required):

Aim: To understand how energy production and recovery might change during an induced episode of post-exertional malaise (PEM) can if these changes might explain a worsening of symptoms after physical exertion.

Participants: 20 people with mild ME/CFS.

Study design: Participants attend two visits:

1. **Initial Visit**
    - Blood sample.
    - Urine sample.
    - MRI.
    - NIRS.
    - Questionnaires.
    - Sub-maximal exercise test to induce an episode of PEM.
2. **Second Visit**
    - 24–48 hours later.
    - Repeat sampling and assessment.

"The purpose of the bike-based sub-max test is to induce mild PEMs within the next 24–48 hours."

Participants then complete questionnaires at home to track PEM onset and severity. When they return — while experiencing PEM — all assessments are repeated.

Why Phase 2 matters: This is the first study to use both MRI and NIRS to directly measure energy production and recovery at the cellular level during PEM. The team expects to see:

- Slower PCr recovery
- Reduced oxygen utilisation
- Evidence of exercise-inflated mitochondrial dysfunction

"Repeated MRI and NIRS experiments while the patients will be in PEM will show even slower energy recovery… suggesting exercise-inflated mitochondrial dysfunction as a contributor to PEM."

These findings could help explain why even small amounts of activity trigger severe symptom flare-ups in ME/CFS.

Laboratory Analyses

Blood and urine samples collected during the study will be stored for future research, including:

- Plasma proteomics (>2000 proteins)
- Metabolomics using state-of-the-art instrumentation at the Rosalind Franklin Institute
- Raman spectroscopy
- Micro-clot quantification
- Investigation of blood-borne factors potentially driving symptoms

Urine samples will also be analysed to try and replicate findings from Professor Maureen Hanson's group in America:

> "Our data suggest that the metabolisms of sedentary individuals who do not have ME/CFS undergo major changes that allow them to recover from exertion, while ME/CFS patients fail to make similar adaptive responses."

https://www.mdpi.com/1422-0067/24/4/3685

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IMPORTANCE OF FUNDING

PEM is one of the most disabling aspects of ME/CFS, yet its biological basis remains unclear. This study will:

- **Addresses the core symptom of ME/CFS.** By investigating mitochondrial function and oxygenation, the research focuses directly on PEM, the most disabling feature of the illness.
- **Use innovative, non-invasive techniques.** MRI and NIRS will allow researchers to study muscle metabolism without invasive biopsies, making participation safer and more acceptable for patients.
- **Builds essential evidence for future trials.** Phase 1 will provide baseline data comparing ME/CFS patients with healthy controls, laying the foundation for Phase 2 and larger-scale studies.
- **Validates a scalable diagnostic tool.** By cross-validating MRI and NIRS, the study could establish NIRS as a lightweight, portable, and cost-effective method for diagnosis and monitoring in clinical practice.
- **Strengthens the UK research ecosystem.** Led by world-class investigators at Oxford, in collaboration with Professor Karl Morten's ME/CFS group and Oxford Brookes University, the project builds on existing expertise and ensures patient involvement throughout.

THE BIG GIVE CHRISTMAS CHALLENEGE

The ME Association would like to thank its supporters for their generosity during last year's Big Give Christmas Challenge which has provided funding for Stage 1 of this important research project.