International Forum on COVID Rehabilitation Research

April 2024

Unlocking the mystery of Post-Exertional Malaise in Long COVID…

Professor Mark Faghy

Before We Begin

I'm here representing a team of experts, dedicated to improving the outcomes of people living with Long COVID..

Lived Experience Experts – we research and work WITH patients, not for them



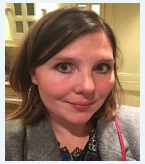
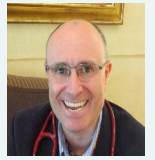



This could be you

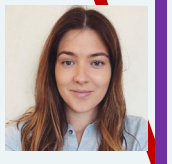


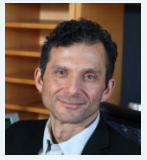


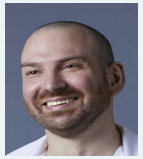

Our MSc/BSc Students ->

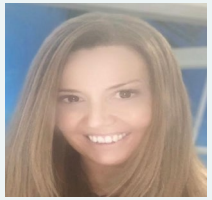













My Friends/The Experts

We are here, we are determined and the door for collaboration is always open...

Talk Overview

- **Our Research into Long COVID**
  - How did we get here..
  - What have we been doing..
- **What is Post-Exertional Malaise (PEM)**
- **The research to increase the understanding of PEM**
  - What we know but what needs to be done
- **Treating and managing PEM**

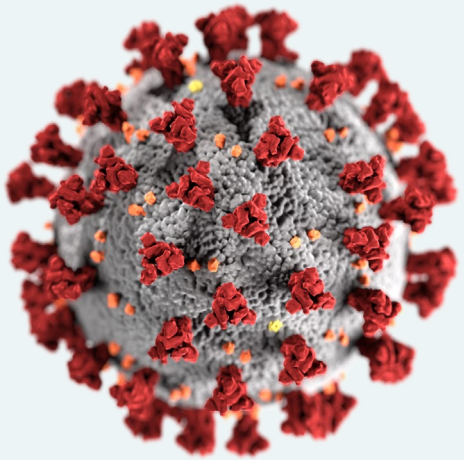
Research Before COVID-19 (BC)

- Started a PhD in Respiratory Physiology (2012)
- Introduced to a local respiratory consultant halfway through…

NHS
University Hospitals of Derby and Burton
NHS Foundation Trust

- We wanted to understand the multi-disciplinary dynamics of recovery better
- Completed several preliminary investigations that concluded in late 2019
- Early 2020 when we went into lockdown, I really struggled being at home.
  - My friends and colleagues were on the frontline

Research Overview (2020-present)



Headline Figures

Collected well over 1 million data points

57 peer-reviewed journal articles

12 Invited conference presentations mostly virtual - but not this one ;-)

£1.8 million research funding

100% proud of the team

But there is still so much to do!!

Patient Advocacy

Completed Projects

- **International Longitudinal Cohort Observation** (2021-2023)
- **Lived Experience Survey(s)** (2021)
- **Outlining Effective Long COVID services** (2022)
- **Systematic review of Long COVID Biomarkers** (2023)

Projects completed and being analysed

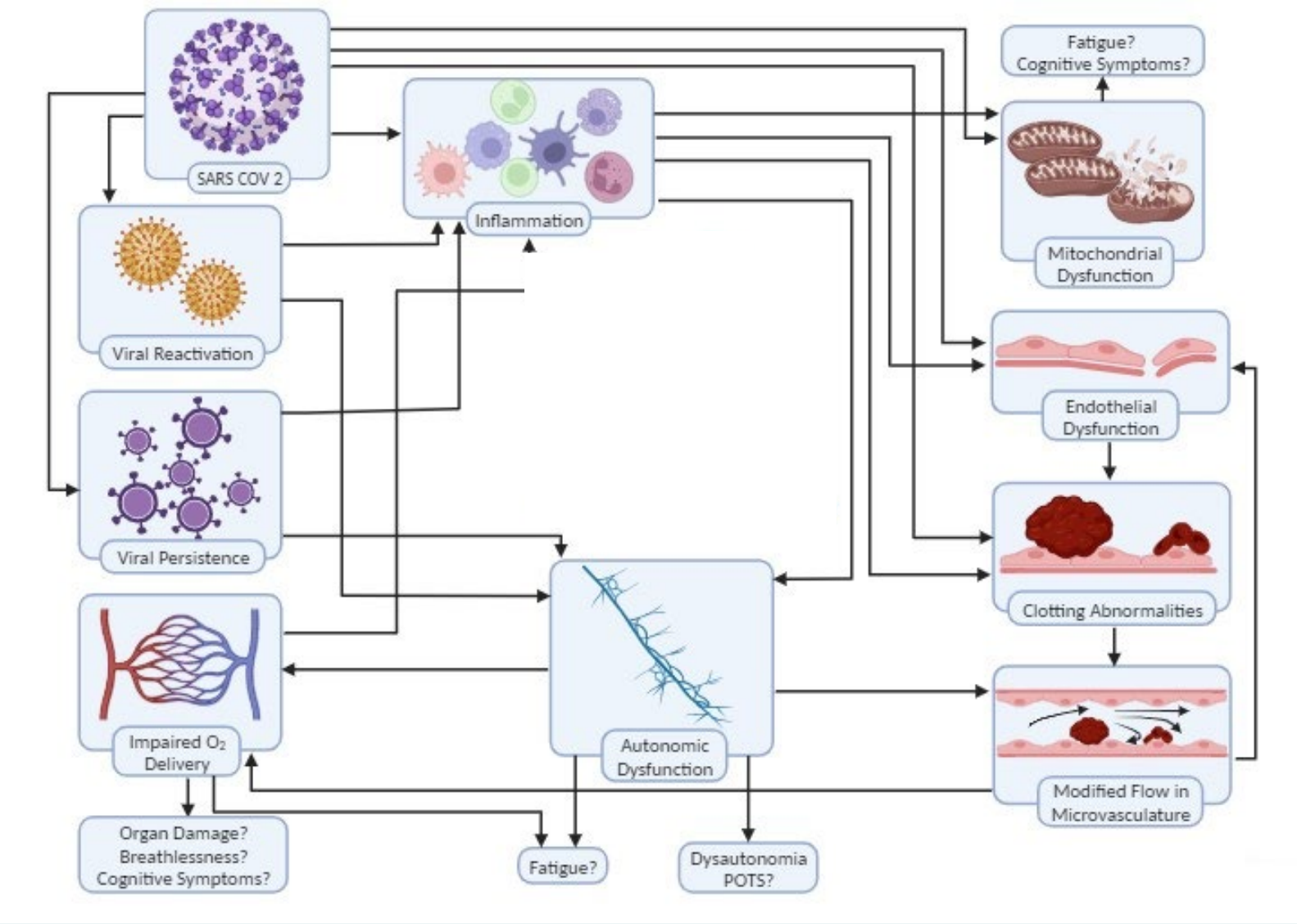
- **2-day CPET and physiological profiling** (2023)
- **Remote symptom tracking using wearable technologies** (2022-2023)
- **Determining Biomarkers for Long COVID** (2023 -2024)

Projects Ongoing

- **Anti-viral medication to improve Long COVID Patient Outcomes** (2024)
- **Developing safe and effective Long COVID Rehabilitation Services** (2024)

****SPOILER** Projects are being planned for 2025 and beyond!**

Long COVID Pathophysiology



[Faghy et al (2024)]

Overview

Long COVID is a multi-system, complex disease.

Associated with a broad, episodic and disabling symptom profile.

Symptoms are highly varied and can relapse unexpectedly.

Increasingly likely that the presentation is linked to more than one pathology

Diagnostic screening and testing are imperative.

Treatment and management strategies will be as complex as the aetiology.

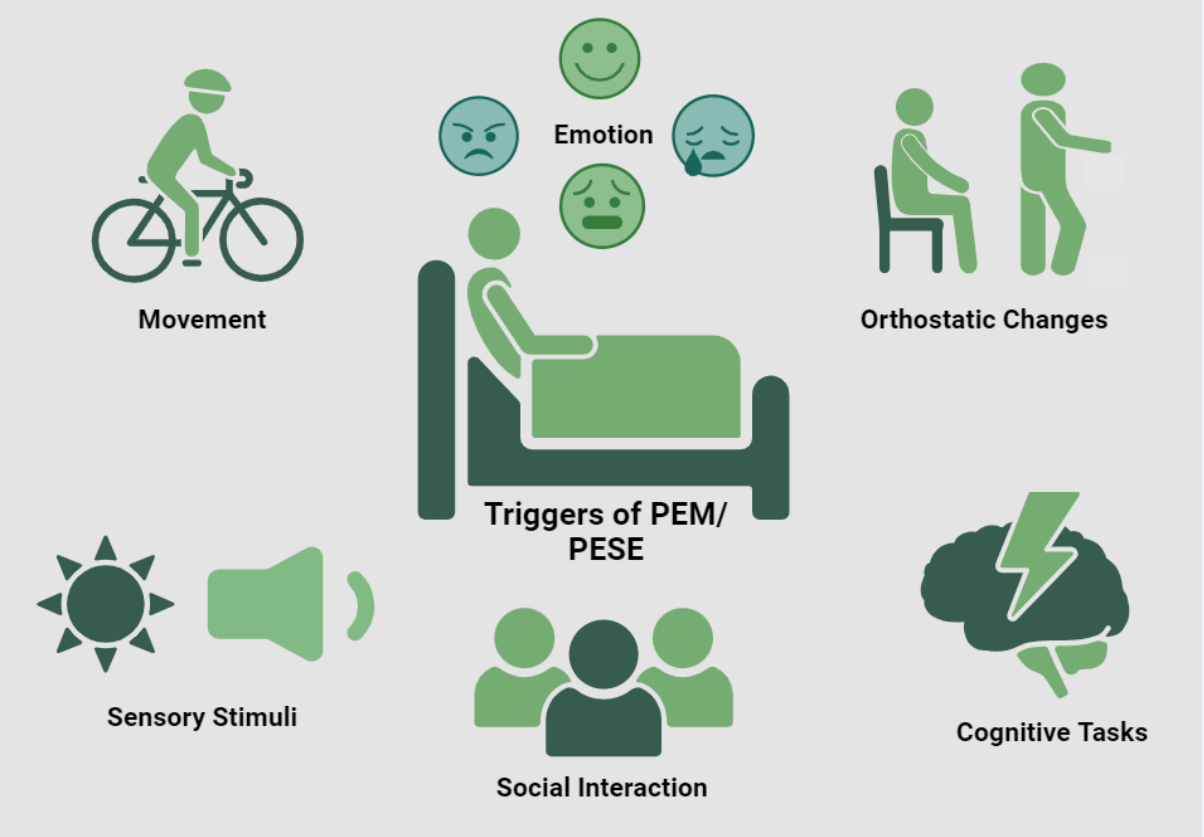
Post-Exertional Malaise (PEM)

Credit Lindsay Skipper for helping create the image.

A multi-factorial symptom that affects multi-factorial around 90% of Long COVID patients.

Defined as a worsening of symptoms that occurs after physical, mental, or orthostatic exertion above an activity threshold.

Inducing PEM can result in a worsening of symptoms that can last from several hours to months



Faghy et al (unpublished)

This threshold varies between Long COVID patients and has not shown to be consistent.

PEM has a drastic impact on functional status and reduces a patient's ability to participate in 'normal' societal activities.

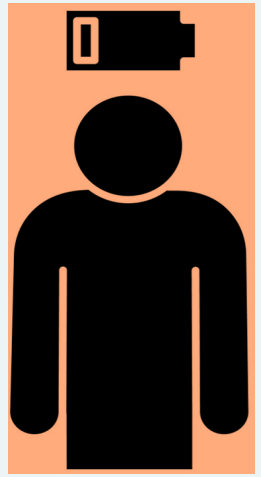
Extreme caution must be taken when prescribing and recommending physical activity as a therapy to increase physical capacity/functional status in patients with Long COVID

The exact pathophysiological contributors to the increased feeling of fatigue and post-exertional malaise are unclear.

The intensity threshold where post-exertional malaise is induced is different between patients and likely relates to the disease severity

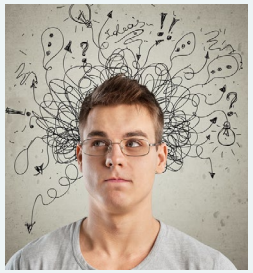
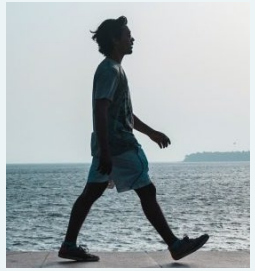
Reduced Thresholds of Tolerance… (Theory)

- **Long-standing history in exercise science domains – known as overtraining!!**
- **Detrimental impact upon bodily function in response to excessive/repeated physiological loading.**
- **Occurs in Long COVID patients following everyday tasks such as taking a shower and walking.**
  - Can last for days, weeks and even months…
- **Threshold testing is a common physiological assessment.**
  - Can be completed using expired gasses/blood lactate and more.
  - Could be used to prevent overstimulating/inducing PEM response.
- **Could allow us to quantify and profile the body's response to external stimuli.**
  - Provide an activity/intensity profile that is within an individual's personal threshold of tolerance
  - Will be complex and must consider the accumulation effect.
  - More research is needed to establish interpersonal variation and to refine personalised thresholds to optimise rehabilitation approaches and understand thresholds.



Reduced Thresholds of Tolerance… Explained

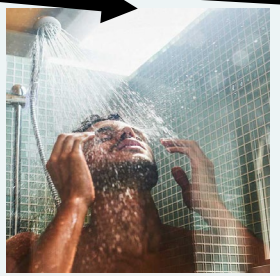
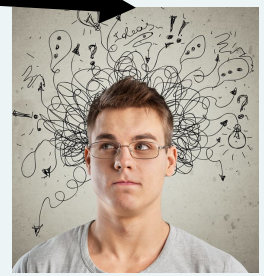
‘Healthy’ Individual

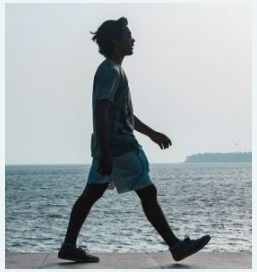





In some instances, these are impossible tasks…

Long COVID Patient




Each patient’s triggers of PEM are very different.

Represents a much smaller threshold of tolerance…

Testing LC Pathophysiology & PEM

- Testing Cardio-respiratory fitness could provide important insight as these methods hold a lot of key information, especially relating to the body's physiological responses and PEM.
- **BUT** this is incredibly difficult as traditional approaches contain exercise testing at intensities that are not appropriate and has a negative impact for patient outcomes/could cause harm.
- So how do we unlock the mystery without exploration?

- **Getting creative over 18 months with:**
  - Experts from around the world – with a shared passion to help people with LC!
  - Detailed and frequent engagement with patients and lived experience experts
  - Lots and lots of zoom meetings on all sorts of time zones
  - Coffee
  - Patience, persistence and a hint of bravery!

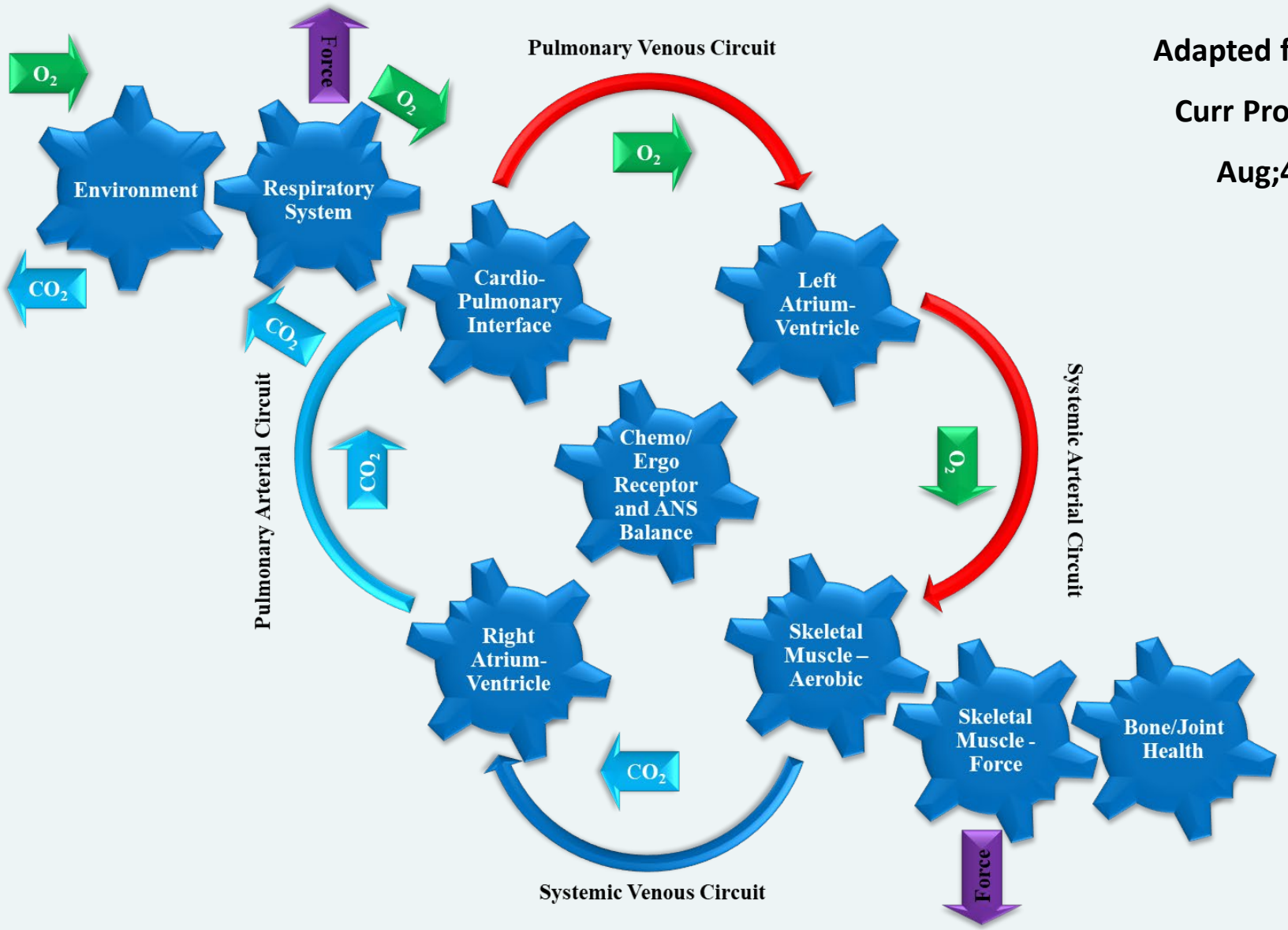
Our Mantra:

To help we must understand..

To understand we must learn..

To learn we must listen.

Physiology of CRF

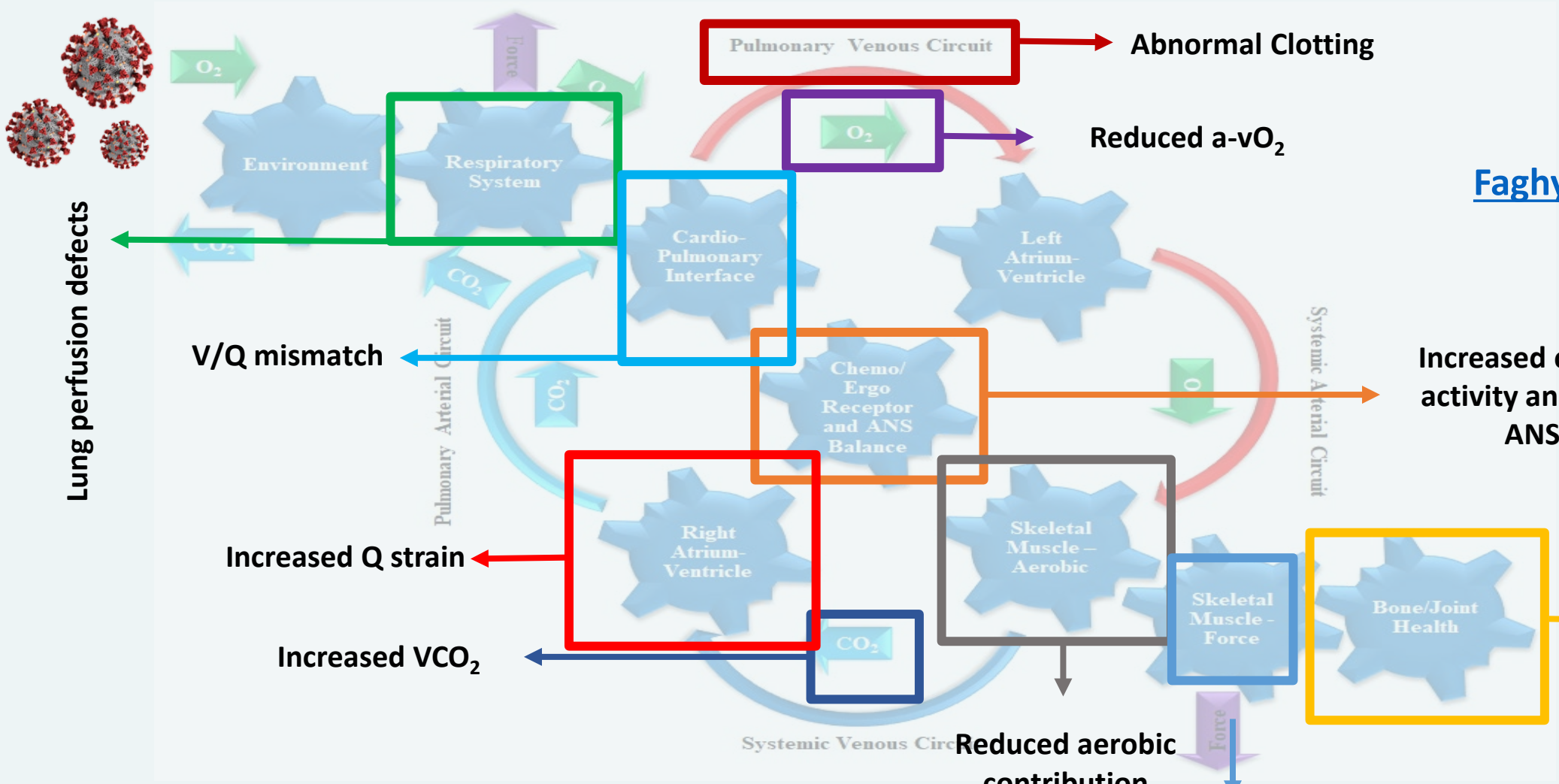


Adapted from Myers et al,

Curr Prob in Card, 2015

Aug;40(8):322-72

Physiology of CRF & LC



Faghy et al (2024)

CPETs in Long COVID

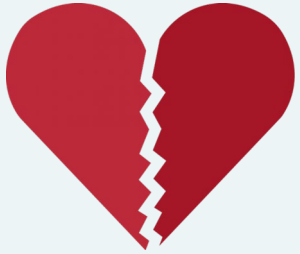
- Devised a sub-maximal, 2-day, incremental protocol
- Patients screened extensively for PEM/risk factors
    - Screened with PROMs and diagnostic testing.
- **Strict inclusion and test termination criteria:**
    - Not suitable for anyone with a moderate/severe PEM risk.
    - Terminated if any feelings of being unwell/dizzy – constant monitoring and observation in place
    - Any cardiac/respiratory indications
    - Test terminated when participant breached anaerobic threshold

CPETs Protocol

- Baseline CPET measures completed over extended period of time
  - Typically 15-20 minutes
  - Could be completed lying supine or seated > mostly seated
- Incremental loading protocol over 12 minute period
  - Opted for a incremental rather than ramp to allow time for indications/events to be deteceted.

- Starting CPET intensity prescribed was prescribed relative to patient functional status, determined via the 6-minute walk test.
  - Strata I: 6MWD < 350 (starting load of 10 watts; with subsequent increments of 5 watts): MAX 70 W
  - Strata II: 6MWD 350 – 400 (starting load of 20w with subsequent increments of 5watts) : MAX 80 W
  - Strata III: 6MWD > 400 (starting load of 30w with subsequent increments of 5 watts): MAX 90 W

Safety Data



- Patients monitored routinely throughout the test for Resp/Q indications
- Symptoms of PEM/PESE monitored remotely via digital app for seven days post test
- The CPET test was well tolerated and adverse event reported throughout the study (0.5%).
- Eighty-four percent of participants completed each 12-minute protocol on subsequent days, with more tests terminated on day 2 due :
  - Low SpO2 - 17%
  - Dyspnoea - 14%
  - Abnormal ECG response - 8%
  - Peripheral limb fatigue - 7%
- Protocol was deemed challenging but tolerable by patients
- Evidence of a mild PEM response in data but no serious exacerbations reported.

Results The analysis is ongoing NOW and at PACE..

Initial Findings Day 1 vs Day 2 comparisons:

- **Cardiorespiratory Fitness**
  - No between-day differences in baseline parameters but clear between-day reduction in CRF (below normative data; peak WR: 85 ± 32 W).
  - Lower $\dot{V}O_2max$ was not due to submaximal effort during the exercise test, as tests satisfied documented guidelines for test termination.
- **Performance Impairment on Day 2**
  - Lower work rate at VT1 in CPET 2 (28±15 W) compared to CPET 1 (33±15 W)
- **Ventilatory Function**
  - Lower maximal ventilation and lower maximal end-tidal partial pressure of CO2 (PETCO2)
- **Stroke Volume**
  - Reduced maximal O2 pulse on CPET 2 (-4.8% - i.e. the product of stroke volume and arteriovenous O2 difference
- **Skeletal Muscle Impairments**
  - Reduced gas exchange threshold and peripheral O2 extraction.

Treating and Managing PEM

- No known/established pharmacological treatments for PEM
- **PACING** is the most established management/preventative technique
- We are working on a plan service plan for effective screening and management of LC – which includes PEM.
  - Tiered approach
  - Clinician led/ patient driven
  - Interdisciplinary – not to be confused with multi-disciplinary
  - Supported by research
  - Has flexibility to address the multi-faceted/dynamic nature of LC to support effectiveness.
- More **funding** and **research** are needed to develop/implement objective assessment of biophysical monitoring into daily routines and rehabilitation services.

To Finish…

- Initial findings give evidence to some of the theories that have been postulated.
- Increasingly likely that all systems are affected and must be understood in isolation and with integrated knowledge.
- Rehabilitation (in its broadest sense) will be complex
  - It must be interdisciplinary and personalised to each patient
- We do not have all the pieces of the puzzle yet..

But we will!!

Thank you!

International Forum on COVID Rehabilitation Research

The door for collaboration is open…

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