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Exercise Pathophysiology in ME/CFS and PASC: More in Common Than Not?

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Abbreviations List

COVID-19: coronavirus disease 2019

CPET: cardiopulmonary exercise test

eSBV: estimated stressed blood volume

iCPET: invasive cardiopulmonary exercise test

ME/CFS: myalgic encephalomyelitis/chronic fatigue syndrome

MAP: mean arterial pressure

mPAP: mean pulmonary artery pressure

niCPET: noninvasive cardiopulmonary exercise test

PASC: post-Acute Sequelae of SARS-CoV-2

PAWP: pulmonary artery wedge pressure

POTS: postural orthostatic tachycardia syndrome

RAP: right atrial pressure

Qc: cardiac output

VO₂: oxygen uptake

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

ABSTRACT

Topic Importance: Post-Acute Sequelae of SARS-CoV-2 (PASC) is a long-term consequence of acute infection from coronavirus disease 2019 (COVID-19). Clinical overlap between PASC and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) has been observed, with shared symptoms including intractable fatigue, postexertional malaise, and orthostatic intolerance. The mechanistic underpinnings of such symptoms are poorly understood.

Review Findings: Early studies suggest deconditioning as the primary explanation for exertional intolerance in PASC. Cardiopulmonary exercise testing (CPET) reveals perturbations related to systemic blood flow and ventilatory control associated with acute exercise intolerance in PASC, which are not typical of simple detraining. Hemodynamic and gas exchange derangements in PASC have substantial overlap with those observed with ME/CFS, suggestive of shared mechanisms.

Summary: This review aims to illustrate exercise pathophysiologic commonalities between PASC and ME/CFS that will help guide future diagnostics and treatment.

INTRODUCTION

Since the onset of the coronavirus disease 2019 (COVID-19) global pandemic, more than 550 million cases of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been recorded. A substantial subset of survivors experiences long-term complications following initial infection, labeled with the all-encompassing term of Post-Acute Sequelae of SARS-CoV-2 (PASC) or colloquially referred to as “long-COVID.” Diagnostic criteria for PASC are not clearly defined and prevalence estimates range from 20 – 50% of survivors. Afflicted patients are often young and have a history of mild acute disease. Given the new and substantial global burden related to PASC, elucidating mechanisms underlying PASC that inform its diagnosis and treatment is critical.¹

PASC is recognized as a multi-system syndrome with a broad range of symptoms, including fatigue, chest pain, exertional dyspnea, post-exertional malaise (PEM), headache, cognitive impairment or “brain fog,” myalgias, and depression.¹ While the etiology of PASC is unknown, proposed mechanisms include, but are not limited to, autoimmune and hyperinflammatory states after acute infection.² Extensive overlap between PASC and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) has been increasingly recognized.³ The

National Academy of Medicine requires three major criteria for diagnosis of ME/CFS: substantial impairment from fatigue for > 6 months, PEM, and unrefreshing sleep, plus either cognitive impairment or orthostatic intolerance.⁴ Given the substantial overlap in symptoms, a common underlying pathophysiology has been suggested.

Noninvasive cardiopulmonary exercise testing (niCPET), with continuous measurement of pulmonary gas exchange, ventilation, and cardiac monitoring during incremental exercise on a cycle ergometer, offers a diagnostic modality capable of quantifying and explaining the exertional intolerance of PASC and ME/CFS. Up to one-third of patients undergoing CPET after recovery from their acute illness from COVID-19 demonstrates a reduction in oxygen uptake (VO_2).^{5,6}

Invasive cardiopulmonary exercise test (iCPET) data suggest similar exercise pathophysiology underlies both PASC and ME/CFS and argue against deconditioning as the sole explanation for exertional intolerance.^{7,8} Such studies suggest systemic vascular abnormalities including decreased venous return and peripheral left-to-right shunting underlie acute exercise intolerance. Combining iCPET with skin biopsy demonstrating decreased small neurite density further suggests dysautonomia underlies vascular dysregulation.⁷ While noninvasive CPET can reveal abnormalities related to aerobic capacity, stroke volume, and ventilatory efficiency,⁹ invasive CPET elucidates mechanistic underpinnings using direct measurements of pulmonary gas exchange, hemodynamics, oxygen delivery and utilization.

The current review aims to illustrate the following: (1) noninvasive CPET assessment of PASC and ME/CFS; (2) invasive CPET assessment of PASC and ME/CFS; (3) commonalities underlying both syndromes including peripheral vascular dysregulation, hyperventilation, and mitochondrial dysfunction; (4) pediatric considerations; (5) and future directions.

LITERATURE SEARCH

Relevant literature was identified via PubMed and were reviewed by the authors for inclusion. The search strategy included the following terms: “myalgic encephalomyelitis/chronic fatigue syndrome,” “post-acute sequelae of SARS-CoV-2,” “PASC,” “cardiopulmonary exercise test,” “dyspnea,” “post-exertional malaise,” “small fiber neuropathy,” and “mitochondrial dysfunction.” Abstracts were reviewed for relevance. Whenever possible, case series were avoided and larger, prospective trials and meta-analyses were preferentially used.

INITIAL EVALUATION

Diagnostics performed on the patient at rest, including pulmonary function tests, chest imaging, electrocardiogram, orthostatic testing, and echocardiogram, are frequently nondiagnostic in both ME/CFS and PASC. Dyspnea on exertion after COVID-19 has a wide differential diagnosis, such as resolving or persistent interstitial lung abnormalities, pulmonary hypertension, chronic thromboembolic disease/pulmonary hypertension, tracheal stenosis from prior intubation, heart failure, neuromuscular weakness, post-ICU syndrome, and deconditioning.¹⁰ Acute cardiovascular complications related to PASC include myocarditis and pericarditis, with cardiac MRI showing persistent myocardial inflammation months after acute illness.¹¹ The focus of this review, however, is on patients with ME/CFS and PASC who do not have intrinsic cardiopulmonary abnormalities and present with unexplained exertional intolerance.

NONINVASIVE CPET

Noninvasive CPET is a valuable tool assessing exercise-related symptoms in ME/CFS and PASC. ME/CFS patients experience an elevated perception of effort and have a reduced peak VO_2 compared to controls.¹² Mildly reduced peak VO_2 has been described in ME/CFS with early anaerobic thresholds (AT) compared to controls. Overall, peak VO_2 in ME/CFS is believed to be 5.2 to 6.5 mL/kg/min lower compared to controls.¹³ Related niCPET findings include inefficient breathing and hyperventilation.⁸ Inefficient ventilation is characterized by an increased value of VE/VCO_2 which physiologically is related to either hyperventilation or failure to normally decrease physiologic dead space to tidal volume fraction (V_D/V_T) during exercise.

Another niCPET variable found in ME/CFS and PASC is chronotropic incompetence. This is of interest given emerging evidence suggesting autonomic dysfunction in ME/CFS patients.¹⁴ However, chronotropic incompetence has not been reproduced in more recent and larger studies.¹³

Serial niCPET in ME/CFS 24 hours apart test the ability of patients to recover and replicate physiological performance over time.¹⁵ The rationale for such an approach relies on the fact

that patients with ME/CFS experience exercise intolerance along with prolonged recovery from exercise and post-exertional aggravation of symptoms, also known as PEM.⁴ Two-day niCPET protocols have found ME/CFS patients have significantly lower peak VO_2 , earlier onset of the anaerobic threshold (AT), and lower work rate parameters on day 2 compared to day 1.^{15,16} A recent meta-analysis identified that: (1) ME/CFS patients have lower exercise tolerance levels of all parameters on the second CPET compared controls; (2) the difference between patients and controls are more pronounced at the AT in relation to peak; and (3) the workload at the AT was different in ME/CFS patients compared to controls.¹⁷

The biological mechanisms that underlie PEM are not well-understood, though CPET has proven useful towards mechanistic exploration. Both maximal and submaximal exercise protocols have been employed to determine behavioral and physiological consequences of acute exercise challenge. These studies have demonstrated symptom exacerbation of variable intensity, type, and duration,¹⁸ impaired pain regulation,¹⁹ altered immune function markers (e.g. cytokines, complement levels, natural killer cells),²⁰ changes in gut microbiome interactions,²¹ disruption of metabolites,²² and altered brain function.²³ Abnormalities in the skeletal muscle exist in ME/CFS patients related to impaired oxygen delivery during exercise and the inability to recover from exercise-induced pH reductions.²⁴

It is clear from these studies that exercise influences multiple physiological systems. However, few studies have directly tested the associations between the physiological and behavioral manifestations of PEM. One recent study reported that neither symptoms nor cardiopulmonary

responses to acute exercise were predictive of PEM in Veterans with Gulf War illness – a disease that overlaps significantly with ME/CFS.²⁵ Furthermore, given the overlap between ME/CFS and PASC along with the observation of PEM in PASC,²⁶ further research into underlying mechanisms is needed.

INVASIVE CARDIOPULMONARY EXERCISE TEST

Protocols for iCPET, hemodynamic measurements, and pulmonary gas exchange measurements have been described previously (Figure 1).²⁷ Briefly, the pulmonary and radial arteries are catheterized with ultrasound and fluoroscopic guidance, then a standard right heart catheterization is performed with oxygen saturation measurements to assess for intracardiac left-to-right shunting. Patients then perform a maximum, incremental, upright exercise on a cycle ergometer as ventilation and pulmonary gas exchange are continuously measured. Hemodynamics, including right atrial pressure (RAP), mean pulmonary artery pressure (mPAP), and mean arterial pressure (MAP) are continuously recorded and averaged throughout the respiratory cycle.²⁸ Pulmonary arterial wedge pressure (PAWP), and arterial and mixed-venous blood gases and pH are measured every minute. RAP and PAWP are measured as the mean of the “a” wave. Cardiac output (Qc) is calculated using the direct Fick principle. Predicted peak values for Qc assume a normal hemoglobin concentration of 14 g/dL, arterial saturation of 100%, and peak mixed venous oxygen saturation of 25%. To correct for anemia, the peak arterial-venous oxygen content difference should approximate the hemoglobin concentration.²⁹

After eliminating pulmonary mechanical limitations to exercise, the iCPET can differentiate central cardiac and peripheral limitations to acute exercise. Central cardiac limitations are due to left heart disease, right heart disease/pulmonary vascular disease, or inadequate cardiac preload, with age-related upper limits of normal defined in the upright position during cycle ergometry versus using flow or cardiac output-corrected pressure slopes, i.e. mPAP/Qc or PAWP/Qc slopes.³⁰⁻³² Peripheral limitations, characterized by impaired systemic oxygen extraction, may be due to mitochondrial myopathy or microcirculatory left-to-right shunts (Figure 2).

Inadequate Biventricular Preload

The normal central exercise response consists of an increase in Qc and stroke volume to support the increased demand of skeletal muscle metabolism. Qc rises as a function of both mechanical mechanisms, i.e., skeletal-muscle and respiratory pumps, and neural mechanisms from parasympathetic withdrawal and sympathetic activation. In response, biventricular filling pressures normally increase from splanchnic vasoconstriction and peripheral venoconstriction, resulting in increased blood volume in the central circulation to support the increase in Qc and stroke volume.³³

Using iCPET, systemic vascular dysregulation appears to be similar in ME/CFS and PASC. In a heterogeneous population referred for iCPET investigation of unexplained exertional intolerance, low biventricular filling pressures, i.e. “preload failure,” explains depressed aerobic

capacity in approximately 20% of patients.³⁴ In studies enriched with PASC⁸ and ME/CFS, preload failure appears to be ubiquitous.⁷

Small fiber neuropathy's (SFN) prevalence appears to be high in PASC and ME/CFS. In one small study, SFN was observed in nearly 90% of patients with PASC.³⁵ One-third of patients with ME/CFS is definitively diagnosed with SFN by PGP9.5-immunolabeled lower-leg epidermal biopsy,⁷ a prevalence similar to that observed in fibromyalgia and postural orthostatic tachycardia syndrome (POTS).³⁶ The prevalence described in ME/CFS may be underestimated due to the use of distal skin biopsies, which may not capture non-length dependent SFN and is age-dependent.³⁷ Small fibers regulate microvascular tone through sympathetic and parasympathetic cholinergic synapses on perivascular myocytes.³⁸ SFN and distal axonopathy can reduce vasoconstriction, as seen with abnormal lower extremity venous pooling upon standing and low norepinephrine release after sympathetic nervous system stimulation in POTS.³⁹

Impaired Systemic Oxygen Extraction

Normally, during intense exercise, sympathetic tone is elevated but “endogenous sympatholysis” due to local vasodilatory substances such as nitric oxide, adenosine, histamine, and prostacyclin decreases systemic vascular resistance and allows for preferential perfusion of the exercising muscle. Acid changes in the muscle capillary right shift the oxygen-hemoglobin dissociation curve and facilitates oxygen offloading to the muscle capillary.⁴⁰

A high-flow state, suggested by an elevated Q_c/VO_2 slope throughout incremental exercise and elevated mixed venous oxygen saturation at peak exercise has been observed in both ME/CFS and PASC.^{7,8} Systemic microcirculatory dysfunction may explain this through peripheral left-to-right shunts. Left-to-right shunts may be explained by dysautonomia, which include distal or proximal small fiber neuropathy or a co-existing ganglionopathy, sometimes associated with autoantibodies to the acetylcholine receptor.⁴¹ Skin biopsies of patients with small fiber neuropathy and fibromyalgia reveal dysregulated arteriovenous blood flow due to abnormal innervation of arteriovenous shunts, enabling oxygenated blood to bypass capillary beds and return unextracted to the venous circulation.⁴² Recent studies have suggested red cell deformability and endothelial dysfunction may compromise microcirculatory oxygen delivery during exercise.^{43,44}

Mitochondrial myopathy has been implicated in both ME/CFS⁴⁵ and PASC⁴⁶ as an explanation of exertional intolerance and can also present with impaired systemic oxygen extraction during iCPET. While Q_c/VO_2 slopes are elevated in both peripheral left-to-right shunts and mitochondrial dysfunction,⁴⁷ the latter's normal peak exercise Q_c can help differentiate the two (Table 1).

Dyspnea on Exertion

Dyspnea on exertion generally results from ventilatory demand that exceeds capacity.⁴⁸ In ME/CFS and PASC without intrinsic lung disease, pulmonary mechanics are not limiting. As noted above, niCPET suggests an association between breathlessness and inefficient

ventilation, i.e., elevated V_E/V_{CO_2} , which by the alveolar ventilation equation is due to hyperventilation and/or increased physiological dead space/tidal volume (V_D/V_T). The iCPET allows direct measurements of both, with radial arterial blood gases allowing minute-to-minute assessment of acid-base status and mixed expired CO_2 from the metabolic cart, with calculation of V_D/V_T through the Bohr equation.

In patients with PASC and ME/CFS without intrinsic cardiopulmonary disease, ventilatory inefficiency and an erratic breathing pattern⁴⁹ are frequently observed and associated with dyspnea. Interestingly, the aberrant increase in V_E/V_{CO_2} is entirely due to hyperventilation and not due to the failure of the V_D/V_T to fall normally.^{8,50} This is in contradistinction to heart failure⁵¹ and PAH,⁵² where ventilatory inefficiency is driven by *both* elevated V_D/V_T and hyperventilation. In patients with heart failure, skeletal muscle group III-IV afferents play an important role in the exaggerated hyper-ventilatory response seen during exercise.⁵¹ These metaboreceptors detect by-products of muscle metabolism and stimulate group III-IV afferents of the spinal cord to the medullary respiratory centers to stimulate ventilation⁵². It is possible that in PASC and ME/CFS, similar to heart failure patients, an exaggerated skeletal muscle metaboreflex drives hyperventilation. This heightened ventilatory response is associated with exertional dyspnea. Respiratory alkalemia causes a leftward shift of oxygen (O_2) dissociation curve, increasing hemoglobin-oxygen affinity, and inhibiting systemic capillary O_2 offloading, contributing to the reduction in peak exercise VO_2 .^{40,50}

Deconditioning

Deconditioning has been implicated as an explanation for exertional intolerance in ME/CFS and PASC.^{5,6} Invasive CPET offers objective evidence *arguing against simple deconditioning* as an explanation for these symptoms. Low peak exercise Qc and higher intracardiac filling pressures are observed in detrained individuals due to cardiac atrophy and decreased ventricular compliance,^{53,54} diametrically opposed to the previously discussed preload failure hemodynamic phenotype. In a similar fashion, peripheral oxygen extraction is little affected by deconditioning.⁵³

Hypovolemia has been offered as an explanation for low intracardiac filling pressures in POTS, ME/CFS, and PASC . The lack of NPO status for iCPET, absence of diuretic and venodilator drug, and increased peak exercise RAP, Qc and VO₂ in a recent randomized, placebo-controlled iCPET study of pyridostigmine in ME/CFS suggest neurovascular dysregulation underlies preload failure, rather than hypovolemia.^{7,8,55}

Special Consideration in Pediatrics

Children with SARS-Cov2 often have asymptomatic or mild disease. However, a minority of pediatric patients have a more severe course either acutely manifesting as ARDS and/or myocarditis or 4-6 weeks later as a post inflammatory disorder known as multi-system inflammatory syndrome in children (MIS-C). For those with MIS-C, illness is severe, with approximately 80% of patients requiring intensive care, approximately 50% showing features of LV systolic dysfunction and myocarditis, 10-20% developing acute coronary artery aneurysms, 20% with EKG abnormalities/arrhythmias, and 4% requiring ECMO.^{56,57}

While many surviving patients return to their baseline health within 8 weeks of their illness, a proportion of children experience chronic health impairments.⁵⁸ Meta-analyses of observational studies including > 80,000 children report long COVID symptoms in 25% of children after SARS-CoV2 infection.⁵⁹ Prominent symptoms include exercise intolerance, shortness of breath, and orthostatic intolerance. Such impairments may be secondary to the severity of illness, post-ICU syndrome, critical illness myopathy, residual cardiac dysfunction, or deconditioning. However, these symptoms also occur in outpatients with mild SARS-CoV2 illness which would be more suggestive of a pathophysiology similar to ME/CFS. Fatigue and

post-exertional malaise are among the most common symptoms reported in children with long COVID. A recent prospective, multicenter study identified persistent symptoms and activity intolerance at 2-4 months after hospitalization for 26.9% of children hospitalized with acute COVID and 30% of those hospitalized with MIS-C.⁶⁰ Meta-analysis also showed these symptoms were among the most common reported in children who were not hospitalized.⁵⁹ PASC symptoms in children may be independent of the severity of the initial infection and occur despite resolution of laboratory and echocardiographic abnormalities.^{60,61}

There are limited data regarding formal exercise testing in patients with PASC or MIS-C. In a group of 40 children followed after hospitalization for MIS-C, 45% had 6-minute walk test performances below the third percentile for their age and sex at 6 months post discharge.⁶² In addition, abnormal cardiorespiratory responses during exercise were demonstrated in a small number of patients after hospitalization for MIS-C. In this sample all patients had lower VO_{2peak} , impaired oxidative metabolism (lower VO_{2VAT} and OUES), and ventilatory inefficiency (higher VE/VCO_2) compared with normal values for the cohort.⁶³

While possibly connected to residual cardiac disease, both impaired 6-minute walk and low VO_{2peak} occurred in some patients who had normal inflammatory markers and normal ventricular systolic function on echocardiogram. It is unclear whether the persistent symptoms of PASC in children may have some contribution from deconditioning as suggested from these healthy control studies or are entirely from the pathobiology of the illness itself.⁶⁴

Shortness of breath has also been reported as a frequent symptom in children with long COVID. A single center study comparing pulmonary function testing in seventy-three children and adolescents after SARS-CoV-2 seroconversion, demonstrated lack of impairment except in those with severe infection and no difference in follow up pulmonary function testing compared with a group of healthy controls.⁶⁵ The mechanisms underlying the discrepancy between subjective persistent respiratory complaints and normal pulmonary function in children with long COVID are unclear but this finding has similarity to what has been reported in ME/CFS.

Orthostatic intolerance, described in most patients with ME/CSF, is a common finding in adolescents with PASC with reported orthostatic symptoms as well as descriptions of palpitations, dizziness and lightheadedness.^{58,61} In some instances post COVID infection, adolescents may be diagnosed with postural tachycardia syndrome (POTS) in the setting of excessive heart rate increase without hypotension while upright or other forms of dysautonomia, reinforcing the importance of orthostatic testing in the evaluation of PASC symptoms in young patients.⁵⁸

In addition to obtaining a careful history of SARS-CoV-2 illness, complications, and comorbidities, testing in children and adolescents with PASC (severe illness as well as mild) should include laboratory analysis, echocardiogram +/- cardiac MRI, PFTs, 6-minute walk test, CPET and orthostatic testing. Ongoing large prospective multicenter trials such as the NIH sponsored Long-term Outcomes after the Multisystem Inflammatory Syndrome in Children

(MUSIC) study and the NIH RECOVER program, studying post-acute sequelae of COVID-19, will be crucial to our understanding of this disease, allowing for more definitive clinical guidelines for management and treatment of children with PASC.

KNOWLEDGE GAPS AND FUTURE DIRECTIONS

Given the significant global burden of ME/CFS and the suspected societal costs of PASC, further research into underlying mechanisms and treatment is needed. Invasive CPET offers insights into underlying pathophysiology of ME/CFS and PASC that cannot be derived from testing of the patient in the resting state or noninvasively. Future directions using noninvasive CPET in conjunction with plasma -omic signatures may be useful. Metabolomics reveal exercise perturbations in lipid-related and energy-related pathways, with commonality observed with glutamate metabolism.²² Metabolic profiles of PASC show elevated ferritin, D-dimer, erythrocyte sedimentation rate, and C-reactive protein, suggestive of a chronic inflammatory state.⁶⁶ Targeting these pathways may offer benefit related to symptom burden.

There are no FDA approved treatments for ME/CFS and PASC. Non-pharmacologic therapies can be offered, though data are based on treating patients with POTS. These include increased dietary salt and fluid intake, activity modification such as leg crossing and squatting, and the use of compression stockings and abdominal binders.⁶⁷ While graded exercise has been recommended for POTS, PEM makes exercise recommendations difficult in ME/CFS and PASC, supporting the role of CPET guided exercise prescriptions in rehabilitation efforts. Prior studies

have evaluated cognitive behavioral therapy, graded exercise,⁶⁸ intravenous immunoglobulin,⁶⁹ and B-cell depletion.⁷⁰ While robust evidence exists for treating autoantibody mediated disease such as myasthenia gravis, limited data support the use of immunosuppression in autoantibody associated ME/CFS.⁷¹ Increasing recognition of mitochondrial dysfunction underlying PASC has led to clinical trials evaluating compounds to improve muscle metabolism (NCT05152849). However, limited efficacy and data exist for the use of mitochondrial supplements such as ubiquinol, alpha-lipoic acid, L-carnitine, oxaloacetate, and B-vitamins, though little harm results from their use.^{72,73} Finally, a double-blind, randomized, placebo-controlled trial of a single dose of pyridostigmine in patients with ME/CFS undergoing iCPET demonstrated improvement in VO_2 by increasing Q_c and right ventricular filling pressures.⁵⁵ Long-term, placebo-controlled studies are needed to assess for improvements in PEM and exercise tolerance.

CONCLUSION

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_2 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.

References

1. Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. *Nat Med*. 2021;27(4):601-615.
2. Bektas A, Schurman SH, Franceschi C, Ferrucci L. A public health perspective of aging: do hyper-inflammatory syndromes such as COVID-19, SARS, ARDS, cytokine storm syndrome, and post-ICU syndrome accelerate short- and long-term inflammaging? *Immun Ageing*. 2020;17:23.
3. Wong TL, Weitzer DJ. Long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)-A Systemic Review and Comparison of Clinical Presentation and Symptomatology. *Medicina (Kaunas)*. 2021;57(5).
4. Clayton EW. Beyond myalgic encephalomyelitis/chronic fatigue syndrome: an IOM report on redefining an illness. *JAMA*. 2015;313(11):1101-1102.
5. Rinaldo RF, Mondoni M, Parazzini EM, et al. Deconditioning as main mechanism of impaired exercise response in COVID-19 survivors. *Eur Respir J*. 2021;58(2).
6. Skjorten I, Ankerstjerne OAW, Trebinjac D, et al. Cardiopulmonary exercise capacity and limitations 3 months after COVID-19 hospitalisation. *Eur Respir J*. 2021;58(2).
7. Joseph P, Arevalo C, Oliveira RKF, et al. Insights From Invasive Cardiopulmonary Exercise Testing of Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Chest*. 2021;160(2):642-651.
8. Singh I, Joseph P, Heerdt PM, et al. Persistent Exertional Intolerance After COVID-19: Insights From Invasive Cardiopulmonary Exercise Testing. *Chest*. 2022;161(1):54-63.
9. Schwendinger F, Knaier R, Radtke T, Schmidt-Trucksass A. Low Cardiorespiratory Fitness Post-COVID-19: A Narrative Review. *Sports Med*. 2023;53(1):51-74.
10. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*. 2021;397(10270):220-232.
11. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5(11):1265-1273.
12. Inbar O, Dlin R, Rotstein A, Whipp BJ. Physiological responses to incremental exercise in patients with chronic fatigue syndrome. *Med Sci Sports Exerc*. 2001;33(9):1463-1470.
13. Cook DB, VanRiper S, Dougherty RJ, et al. Cardiopulmonary, metabolic, and perceptual responses during exercise in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): A Multi-site Clinical Assessment of ME/CFS (MCAM) sub-study. *PLoS One*. 2022;17(3):e0265315.
14. Nelson MJ, Buckley JD, Thomson RL, Bellenger CR, Davison K. Markers of Cardiac Autonomic Function During Consecutive Day Peak Exercise Tests in People With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Front Physiol*. 2021;12:771899.

15. Stevens S, Snell C, Stevens J, Keller B, VanNess JM. Cardiopulmonary Exercise Test Methodology for Assessing Exertion Intolerance in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Front Pediatr*. 2018;6:242.
16. Keller BA, Pryor JL, Giloteaux L. Inability of myalgic encephalomyelitis/chronic fatigue syndrome patients to reproduce VO₂ peak indicates functional impairment. *J Transl Med*. 2014;12:104.
17. Lim EJ, Kang EB, Jang ES, Son CG. The Prospects of the Two-Day Cardiopulmonary Exercise Test (CPET) in ME/CFS Patients: A Meta-Analysis. *J Clin Med*. 2020;9(12).
18. White AT, Light AR, Hughen RW, et al. Severity of symptom flare after moderate exercise is linked to cytokine activity in chronic fatigue syndrome. *Psychophysiology*. 2010;47(4):615-624.
19. Van Oosterwijck J, Nijs J, Meeus M, et al. Pain inhibition and postexertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome: an experimental study. *J Intern Med*. 2010;268(3):265-278.
20. Smylie AL, Broderick G, Fernandes H, et al. A comparison of sex-specific immune signatures in Gulf War illness and chronic fatigue syndrome. *BMC Immunol*. 2013;14:29.
21. Shukla SK, Cook D, Meyer J, et al. Changes in Gut and Plasma Microbiome following Exercise Challenge in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). *PLoS One*. 2015;10(12):e0145453.
22. Germain A, Giloteaux L, Moore GE, et al. Plasma metabolomics reveals disrupted response and recovery following maximal exercise in myalgic encephalomyelitis/chronic fatigue syndrome. *JCI Insight*. 2022;7(9).
23. Cook DB, Light AR, Light KC, et al. Neural consequences of post-exertion malaise in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Brain Behav Immun*. 2017;62:87-99.
24. McCully KK, Natelson BH. Impaired oxygen delivery to muscle in chronic fatigue syndrome. *Clin Sci (Lond)*. 1999;97(5):603-608; discussion 611-603.
25. Boruch AE, Lindheimer JB, Klein-Adams JC, et al. Predicting post-exertional malaise in Gulf War Illness based on acute exercise responses. *Life Sci*. 2021;280:119701.
26. Twomey R, DeMars J, Franklin K, Culos-Reed SN, Weatherald J, Wrightson JG. Chronic Fatigue and Postexertional Malaise in People Living With Long COVID: An Observational Study. *Phys Ther*. 2022;102(4).
27. Maron BA, Cockrill BA, Waxman AB, Systrom DM. The invasive cardiopulmonary exercise test. *Circulation*. 2013;127(10):1157-1164.
28. Boerrigter BG, Waxman AB, Westerhof N, Vonk-Noordegraaf A, Systrom DM. Measuring central pulmonary pressures during exercise in COPD: how to cope with respiratory effects. *European Respiratory Journal*. 2014;43(5):1316-1325.
29. Wasserman K. *Principles of exercise testing and interpretation : including pathophysiology and clinical applications*. 5th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012.
30. Oliveira RK, Agarwal M, Tracy JA, et al. Age-related upper limits of normal for maximum upright exercise pulmonary haemodynamics. *Eur Respir J*. 2016;47(4):1179-1188.
31. Zeder K, Banfi C, Steinrissler-Alex G, et al. Diagnostic, prognostic and differential-diagnostic relevance of pulmonary hemodynamics during exercise - a systematic review. *Eur Respir J*. 2022.
32. Eisman AS, Shah RV, Dhakal BP, et al. Pulmonary Capillary Wedge Pressure Patterns During Exercise Predict Exercise Capacity and Incident Heart Failure. *Circ Heart Fail*. 2018;11(5):e004750.
33. Nobrega AC, O'Leary D, Silva BM, Marongiu E, Piepoli MF, Crisafulli A. Neural regulation of cardiovascular response to exercise: role of central command and peripheral afferents. *Biomed Res Int*. 2014;2014:478965.

34. Oldham WM, Lewis GD, Opotowsky AR, Waxman AB, Systrom DM. Unexplained exertional dyspnea caused by low ventricular filling pressures: results from clinical invasive cardiopulmonary exercise testing. *Pulm Circ.* 2016;6(1):55-62.
35. Novak P, Mukerji SS, Alabsi HS, et al. Multisystem Involvement in Post-Acute Sequelae of Coronavirus Disease 19. *Ann Neurol.* 2022;91(3):367-379.
36. Oaklander AL, Herzog ZD, Downs HM, Klein MM. Objective evidence that small-fiber polyneuropathy underlies some illnesses currently labeled as fibromyalgia. *Pain.* 2013;154(11):2310-2316.
37. Evdokimov D, Frank J, Klitsch A, et al. Reduction of skin innervation is associated with a severe fibromyalgia phenotype. *Ann Neurol.* 2019;86(4):504-516.
38. Schuller TB, Hermann K, Baron R. Quantitative assessment and correlation of sympathetic, parasympathetic, and afferent small fiber function in peripheral neuropathy. *J Neurol.* 2000;247(4):267-272.
39. Jacob G, Costa F, Shannon JR, et al. The neuropathic postural tachycardia syndrome. *N Engl J Med.* 2000;343(14):1008-1014.
40. Stringer W, Wasserman K, Casaburi R, Porszasz J, Maehara K, French W. Lactic acidosis as a facilitator of oxyhemoglobin dissociation during exercise. *J Appl Physiol (1985).* 1994;76(4):1462-1467.
41. Nakane S, Mukaino A, Higuchi O, et al. A comprehensive analysis of the clinical characteristics and laboratory features in 179 patients with autoimmune autonomic ganglionopathy. *J Autoimmun.* 2020;108:102403.
42. Albrecht PJ, Hou Q, Argoff CE, Storey JR, Wymer JP, Rice FL. Excessive peptidergic sensory innervation of cutaneous arteriole-venule shunts (AVS) in the palmar glabrous skin of fibromyalgia patients: implications for widespread deep tissue pain and fatigue. *Pain Med.* 2013;14(6):895-915.
43. Saha AK, Schmidt BR, Wilhelmy J, et al. Red blood cell deformability is diminished in patients with Chronic Fatigue Syndrome. *Clin Hemorheol Microcirc.* 2019;71(1):113-116.
44. Sandvik MK, Sørland K, Leirgul E, et al. Endothelial dysfunction in ME/CFS patients. *PLOS ONE.* 2023;18(2):e0280942.
45. Wawrzyniak NR, Joseph AM, Levin DG, et al. Idiopathic chronic fatigue in older adults is linked to impaired mitochondrial content and biogenesis signaling in skeletal muscle. *Oncotarget.* 2016;7(33):52695-52709.
46. de Boer E, Petrache I, Goldstein NM, et al. Decreased Fatty Acid Oxidation and Altered Lactate Production during Exercise in Patients with Post-acute COVID-19 Syndrome. *Am J Respir Crit Care Med.* 2022;205(1):126-129.
47. Taivassalo T, Jensen TD, Kennaway N, DiMauro S, Vissing J, Haller RG. The spectrum of exercise tolerance in mitochondrial myopathies: a study of 40 patients. *Brain.* 2003;126(Pt 2):413-423.
48. O'Donnell DE, Ora J, Webb KA, Laveneziana P, Jensen D. Mechanisms of activity-related dyspnea in pulmonary diseases. *Respir Physiol Neurobiol.* 2009;167(1):116-132.
49. Mancini DM, Brunjes DL, Lala A, Trivieri MG, Contreras JP, Natelson BH. Use of Cardiopulmonary Stress Testing for Patients With Unexplained Dyspnea Post-Coronavirus Disease. *JACC Heart Fail.* 2021;9(12):927-937.
50. Melamed KH, Santos M, Oliveira RKF, et al. Unexplained exertional intolerance associated with impaired systemic oxygen extraction. *Eur J Appl Physiol.* 2019;119(10):2375-2389.
51. Lalande S, Cross TJ, Keller-Ross ML, Morris NR, Johnson BD, Taylor BJ. Exercise Intolerance in Heart Failure: Central Role for the Pulmonary System. *Exerc Sport Sci Rev.* 2020;48(1):11-19.
52. Li J, Hand GA, Potts JT, Wilson LB, Mitchell JH. c-Fos expression in the medulla induced by static muscle contraction in cats. *Am J Physiol.* 1997;272(1 Pt 2):H48-56.

53. Saltin B, Blomqvist G, Mitchell JH, Johnson RL, Jr., Wildenthal K, Chapman CB. Response to exercise after bed rest and after training. *Circulation*. 1968;38(5 Suppl):VII1-78.
54. Stickland MK, Welsh RC, Petersen SR, et al. Does fitness level modulate the cardiovascular hemodynamic response to exercise? *J Appl Physiol (1985)*. 2006;100(6):1895-1901.
55. Joseph P, Pari R, Miller S, et al. Neurovascular Dysregulation and Acute Exercise Intolerance in ME/CFS: A Randomized, Placebo-Controlled Trial of Pyridostigmine. *Chest*. 2022.
56. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. *N Engl J Med*. 2020;383(4):334-346.
57. Capone CA, Subramony A, Sweberg T, et al. Characteristics, Cardiac Involvement, and Outcomes of Multisystem Inflammatory Syndrome of Childhood Associated with severe acute respiratory syndrome coronavirus 2 Infection. *J Pediatr*. 2020;224:141-145.
58. Morrow AK, Malone LA, Kokorelis C, et al. Long-Term COVID 19 Sequelae in Adolescents: the Overlap with Orthostatic Intolerance and ME/CFS. *Curr Pediatr Rep*. 2022;10(2):31-44.
59. Lopez-Leon S, Wegman-Ostrosky T, Ayuzo Del Valle NC, et al. Long-COVID in children and adolescents: a systematic review and meta-analyses. *Sci Rep*. 2022;12(1):9950.
60. Maddux AB, Berbert L, Young CC, et al. Health Impairments in Children and Adolescents After Hospitalization for Acute COVID-19 or MIS-C. *Pediatrics*. 2022.
61. Townsend L, Dyer AH, Jones K, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. *PLoS One*. 2020;15(11):e0240784.
62. Penner J, Abdel-Mannan O, Grant K, et al. 6-month multidisciplinary follow-up and outcomes of patients with paediatric inflammatory multisystem syndrome (PIMS-TS) at a UK tertiary paediatric hospital: a retrospective cohort study. *Lancet Child Adolesc Health*. 2021;5(7):473-482.
63. Astley C, Badue Pereira MF, Lima MS, et al. In-depth cardiovascular and pulmonary assessments in children with multisystem inflammatory syndrome after SARS-CoV-2 infection: A case series study. *Physiol Rep*. 2022;10(5):e15201.
64. Burstein DS, Edelson J, O'Malley S, et al. Cardiopulmonary Exercise Performance in the Pediatric and Young Adult Population Before and During the COVID-19 Pandemic. *Pediatr Cardiol*. 2022.
65. Knoke L, Schlegtendal A, Maier C, Eitner L, Lucke T, Brinkmann F. Pulmonary Function and Long-Term Respiratory Symptoms in Children and Adolescents After COVID-19. *Front Pediatr*. 2022;10:851008.
66. Pasini E, Corsetti G, Romano C, et al. Serum Metabolic Profile in Patients With Long-Covid (PASC) Syndrome: Clinical Implications. *Front Med (Lausanne)*. 2021;8:714426.
67. Wieling W, Kaufmann H, Claydon VE, et al. Diagnosis and treatment of orthostatic hypotension. *Lancet Neurol*. 2022;21(8):735-746.
68. Wilshire CE, Kindlon T, Courtney R, et al. Rethinking the treatment of chronic fatigue syndrome- a reanalysis and evaluation of findings from a recent major trial of graded exercise and CBT. *BMC Psychol*. 2018;6(1):6.
69. Rowe KS. Double-blind randomized controlled trial to assess the efficacy of intravenous gammaglobulin for the management of chronic fatigue syndrome in adolescents. *J Psychiatr Res*. 1997;31(1):133-147.
70. Fluge O, Rekeland IG, Lien K, et al. B-Lymphocyte Depletion in Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Randomized, Double-Blind, Placebo-Controlled Trial. *Ann Intern Med*. 2019;170(9):585-593.
71. Liu X, Treister R, Lang M, Oaklander AL. IVIg for apparently autoimmune small-fiber polyneuropathy: first analysis of efficacy and safety. *Ther Adv Neurol Disord*. 2018;11:1756285617744484.

72. Parikh S, Goldstein A, Koenig MK, et al. Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. *Genet Med*. 2015;17(9):689-701.
73. Cash A, Kaufman DL. Oxaloacetate Treatment For Mental And Physical Fatigue In Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Long-COVID fatigue patients: a non-randomized controlled clinical trial. *J Transl Med*. 2022;20(1):295.

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Table 1 – Differential Diagnosis of Changes in Peak Exercise Oxygen Uptake and Cardiac Output

	VO ₂ Peak	Peak Q _c	Diagnosis
Athletic Heart	↑	↑	Commensurate increases in VO ₂ and Q _c at peak exercise is characteristic of endurance trained athletes
Preload Failure	↓	↓	Depressed VO ₂ and Q _c at peak exercise in the absence of a pulmonary mechanical limit suggests preload failure
L to R Shunt	↓	↑	Depressed VO ₂ peak and supranormal Q _c peak is a hallmark of left to right shunting
Mitochondrial Dysfunction	↓	↔	Depressed VO ₂ peak and normal Q _c peak suggests mitochondrial dysfunction without cardiac involvement

VO₂: Oxygen Uptake; Q_c: Cardiac Output

Figure 1 – Invasive Cardiopulmonary Exercise Test

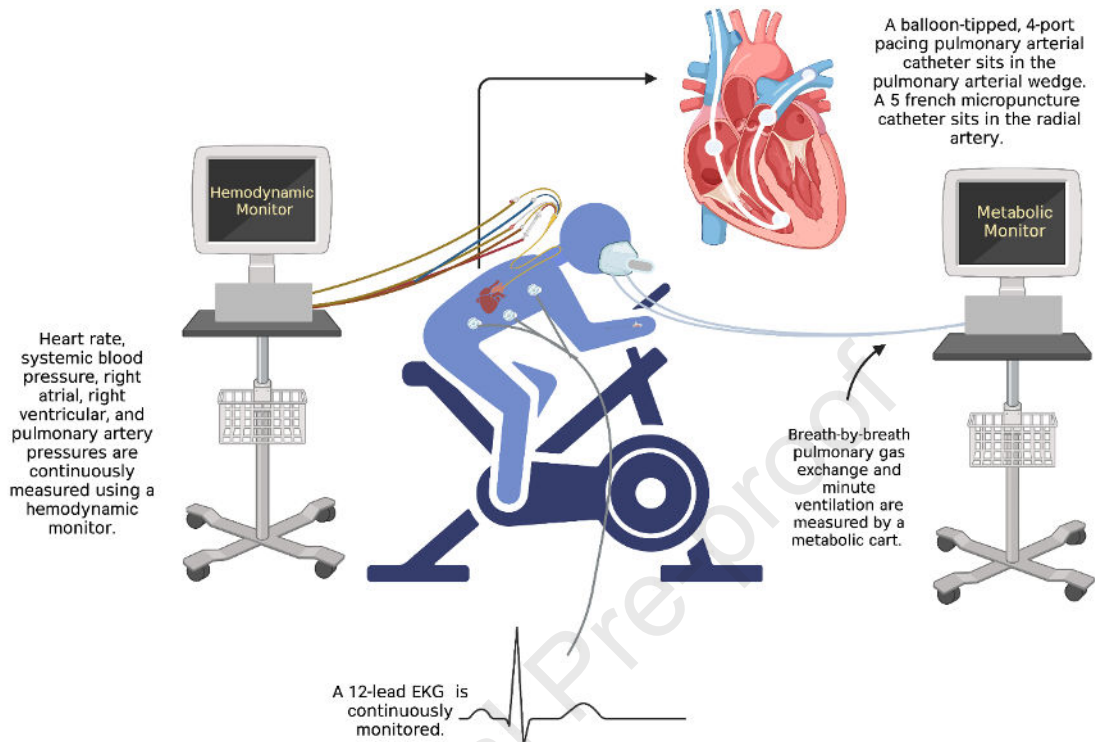
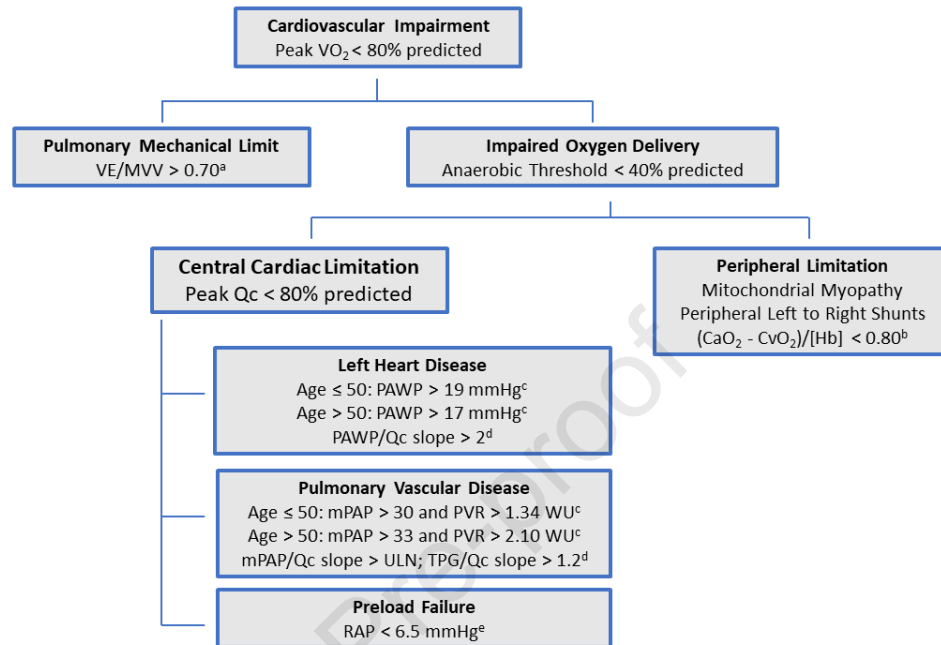


Figure 2 – Evaluation of Undifferentiated Exertional Intolerance

CaO₂: Arterial oxygen content. CvO₂: Venous oxygen content. Hb: Hemoglobin. mPAP: Mean pulmonary artery pressure. PAWP: Pulmonary artery wedge pressure. PVR: Pulmonary vascular resistance. MVV: Maximum voluntary ventilation. RAP: Right atrial pressure. Qc: Cardiac output. VE: Minute ventilation. VO₂: Oxygen uptake

^aBreathing Reserve Index¹

^bPeripheral Limitation²

^cAge defined upper limits of normal³

^dThe mPAP/Qc slope is age-dependent whereas the TPG/Qc slope is age-independent.⁴

^ePreload failure⁵

1. Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis*. 1984;129(2 Pt 2):S49-55.
2. Wasserman K. *Principles of exercise testing and interpretation : including pathophysiology and clinical applications*. 5th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012.
3. Oliveira RK, Agarwal M, Tracy JA, et al. Age-related upper limits of normal for maximum upright exercise pulmonary haemodynamics. *Eur Respir J*. 2016;47(4):1179-1188.
4. Zeder K, Banfi C, Steinrissler-Alex G, et al. Diagnostic, prognostic and differential-diagnostic relevance of pulmonary hemodynamics during exercise – a systematic review. *European Respiratory Journal*. 2022:2103181.

5. Oldham WM, Lewis GD, Opatowsky AR, Waxman AB, Systrom DM. Unexplained exertional dyspnea caused by low ventricular filling pressures: results from clinical invasive cardiopulmonary exercise testing. *Pulm Circ.* 2016;6(1):55-62.

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