**Inspiratory Muscle Training for Post-COVID Syndrome**

**By**

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**Proposal for Dissertation Research**

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# Introduction

## Background

### - Definition

- Prevalence

## Pathophysiology

### Respiratory

During the acute stage of infection, COVID-19 virus can induce myopathic changes by directly binding to ACE-2 receptors <CITATION>, leading to widespread symptoms of myalgia <CITATION>. While all regions of the musculoskeletal system are vulnerable, the diaphragm is particularly vulnerable due to increased proportion of ACE-2 <CITATION>. Thus, weakness of the respiratory musculature occurs frequently in the months immediately following COVID-19 infection <CITATION>. For instance, an analysis by <EXAMPLE>.

These respiratory deficits persist in PCS. During inhalation, PCS patients demonstrate reduced maximum inspiratory pressure (MIP) (McNarry et al., 2022).

Importantly, the respiratory deficits identified in PCS do not spontaneously resolve over time. For instance, a study using twitch transdiaphragmatic pressure – the gold standard assessment of diaphragm contractility <CITATION> – found insignificant improvement between 14 months and 31 months post-infection (Spiesshoefer et al., 2024). Interestingly, improvement was observed in Diaphragm Voluntary Activity Index (DVAI) and Sniff Pes-Pdi, indicating that patients were gradually regaining voluntary control of the diaphragm during their recovery period but were still limited in maximum force production capacity. These findings are consistent with an underlying pathology of viral-induced diaphragm myopathy.

### Vascular

Along with the respiratory musculature, endothelial cells lining the vascular walls are rich in ACE-2 inhibitors and vulnerable to attack from COVID-19 virus <CITATION>.

These vascular deficits persist in PCS. Compared to healthy controls, PCS patients have been demonstrated to exhibit reduced markers of macrovascular health including flow-mediated dilation (FMD) (Ambrosino, 2021; Ergül et al., 2022; Riou, 2021) endothelial quotient index (Charfeddine et al., 2021), and increased circulating endothelial cell (CEC) counts (Chioh et al., 2021). For instance, an analysis by <EXAMPLE>.

Ultimately, these endothelial deficits have been associated with a wide range of negative outcomes, During exercise, patients with low FMD are more likely to exhibit poor VO2max, reduced end-tidal CO2, and higher VE/VCO2 slope (Ambrosino et al., 2022). When examining patient subjective symptoms, reduced FMD is associated with increased likelihood of fatigue or neurocognitive dysfunction (Charfeddine et al., 2021).

Along with macrovascular deficits, long COVID has also been associated with damage to the capillaries. PCS patients demonstrated 41% less capillary recruitment compared to healthy controls, and capillary density was particularly reduced in subjects reporting symptoms of neurocognitive fatigue (Osiaevi et al., 2023).

### Exercise Capacity

PCS has been associated with a wide range of impairments to exercise capacity. During tests of physical function, such as the 6 Minute Walk Test (6MWT), PCS patients score lower compared to healthy control participants (Paradowska-Nowakowska et al., 2023). The lower the 6MWT scores, the more likely these subjects were to report symptoms of fatigue and dyspnea (Paradowska-Nowakowska et al., 2023). Cardiopulmonary exercise testing (CPET), which is considered to be the gold standard form of assessment of exercise capacity <CITATION>, stark differences between PCS and healthy control subjects have been revealed. Particularly, vo2max – a marker of overall aerobic function that is associated with a wide range of health metrics <CITATION> -- is disturbingly low in patients with PCS (Barbagelata et al., 2022) (Baratto et al., 2021) (Contreras et al., 2023) (Durstenfeld et al., 2022) (Ambrosino et al., 2022) (Cherneva et al., 2025). In some estimates, 61% of PCS patients exhibit impaired cardiorespiratory fitness (<70% of predicted) compared to 17% of healthy controls (Baratto et al., 2021). According to a meta-analysis of 9 studies, PCS is associated with a mean reduction of 4.9 mL/min/kg in peak VO2. Furthermore, during testing, overall workload and VO2 / work slope is reduced (Baratto et al., 2021).

Subjectively, PCS patients report a greater degree of physical exertion during exercise testing as measured by the Berg <CITATION>. Consequently, a notably large portion of PCS patients are unable to tolerate activity to the point of reaching anaerobic threshold (AT). In a study by Barbagelata, only 50.9% of PCS patients reached AT compared to 72.7% of healthy controls (Barbagelata et al., 2022). Similarly, an analysis by Cherneva et al. found only 48.2% of moderate-to-severe cases of PCS patients reached AT compared to 75% of mild cases and 87.% of healthy controls (Cherneva et al., 2025)

### Autonomic

At rest, PCS patients demonstrate worsened metrics of heart rate variability (HRV) including SDNN, RMSSD, RR Tri, TINN, LF, LF/HF, SD1, ApEN (Santos-de-Araújo et al., 2024).

During exercise, chronotropic incompetence has been identified among PCS patients (Contreras et al., 2023) (Baratto et al., 2021). For instance, an analysis by Contreras et al. indicated that 44% of PCS patients exhibited chronotropic incompetence during CPET compared to only 34% of healthy control subjects (Contreras et al., 2023).

## Symptoms

### Fatigue

Fatigue continues to persist without resolution. For instance, a longitudinal study by Spiesshoefer et al. 2024 found that self-reported fatigue remains elevated 14 months following COVID-19 infection, and these levels show no improvement by 31 months post-infection (Spiesshoefer et al., 2024).

Surprisingly, although PCS is often characterized by disordered sleep,

### Neurocognitive Dysfunction

Neurocognitive dysfunction, commonly referred to as “brain fog”, is regularly described by PCS patients as one of the most debilitating symptoms (Vyas et al., 2022)(Jennings et al., 2022)(Asadi-Pooya et al., 2023) (Orfei et al., 2022)(Nordvig et al., 2023)(Davis et al., 2021)(Sa et al., 2024). Although prevalence estimates vary by cohort, multiple reports indicate that approximately two-thirds of subjects with PCS report neuro-cognitive dysfunctions including problems with attention, executive functioning, problem-solving, memory, and decision-making (Davis et al., 2021)(Jennings et al., 2022). Given the increased mental and physical burden imposed by these symptoms, it is of no wonder that neurocognitive dysfunction has been associated with reduced physical activity, social isolation, and disability (Nordvig et al., 2023).

### Dyspnea

Dyspnea is common among PCS patients (Harenwall et al., 2022) (Paradowska-Nowakowska et al., 2023) (Jennings et al., 2022) (Bulla et al., 2023). Given that diaphragm weakness persists for 31 months following infection with no improvement, it is of little surprise that patients do not report spontaneous resolution of dyspnea symptoms during this time frame (Spiesshoefer et al., 2024).

During exercise, 52.7% report symptoms of dyspnea compared to only 13.7% of healthy controls (Barbagelata et al., 2022).

### Sleep

A large portion of patients with PCS report significantly impaired sleep (Davis et al., 2021)(Sa et al., 2024). Approximately 10-20% of PCS patients have reported a diagnosis of obstructive sleep apnea (Davis et al., 2021) (Riou, 2021). Additionally, PCS patients report additional sleep difficulties including insomnia (Jennings et al., 2022)(Nordvig et al., 2023)(Davis et al., 2021) and nightmares (Davis et al., 2021).

### Functional Capacity

* + - * Back Pain
      * Neck Pain
      * Physical Activity
      * Quality of Life
      * Employment

Overall, patients with PCS report significantly reduced quality of life (Oh et al., 2024).

### Mental Health

PCS is associated with high prevalence of mental health conditions including anxiety (Frésard et al., 2022) (Oh et al., 2024)(Bonner-Jackson et al., 2024), depression (Jennings et al., 2022) (Bonner-Jackson et al., 2024)(Oh et al., 2024), and PSTD (Jennings et al., 2022)(Harenwall et al., 2022).

## Respiratory Influence

### Respiratory Effects on Endothelial Dysfunction

### Respiratory Effects on Exercise Capacity

Respiratory dysfunction has the potential to serve as a major limiting factor of exercise capacity in PCS patients. An analysis by Frésard et al. examined 51 PCS patients during CPET and concluded that 84.3% were limited by dysfunctional breathing or respiratory limitation, compared to only 11.8% who were limited by oxygen delivery and utilization (Frésard et al., 2022). These findings are supported by additional studies that have observed abnormal ventilatory patterns in PCS, including lower tidal volume (Baratto et al., 2021), higher respiratory rates (Baratto et al., 2021), reduced end-tidal CO2 (Baratto et al., 2021)(Ambrosino et al., 2022), lower peak minute ventilation (Contreras et al., 2023)(Baratto et al., 2021), and elevated VE/VCO2 ratio (Baratto et al., 2021)(Ambrosino et al., 2022). Moreoever, reduced end-tidal CO2 values have been directly linked with increased risk for symptoms of post-exertional malaise (Thomas et al., 2025). Collectively, these data suggest that ventilatory dysfunction may play a central role in limiting exercise tolerance among patients with PCS.

### Respiratory Effects on Autonomic Nervous System

### Respiratory Effects on Dyspnea

The diaphragm is the primary muscle of inspiration, and weakness of the diaphragm musculature can be directly responsible for chronic dyspnea <CITATION>. In PCS patients, a longitudinal analysis determined that severity of dyspnea is directly and strongly associated with severity of diaphragm weakness, and that longitudinal improvements in diaphragm strength associate with improvements in self-reported breathing (Spiesshoefer et al., 2024).

### Respiratory Effects on Fatigue and Neurocognitive Dysfunction

Despite the severe and debilitating neurocognitive symptoms reported by patients with PCS, MRI of the cerebrum has identified abnormalities in only a small percentage of subjects reporting cognitive dysfunction (Davis et al., 2021), Similarly, no cerebral pathology has been identified that has associated with chronic and debilitating fatigue.

Rather than cerebral damage, one potential pathophysiological explanation may be weakness to the diaphragm.

Symptoms of dyspnea have been identified to be associated with increased likelihood of experiencing brain fog. For instance, an analysis by Bulla et al. found that 37.5% of PCS patients with neurocognitive dysfunction reported major signs of dyspnea, compared to only 6.3% of patients without neurocognitive dysfunction (Bulla et al., 2023). Similarly, Nordvig et al. found that 48% of patients with neurocognitive dysfunction reported dyspnea compared to 18% without (Nordvig et al., 2023).

### Respiratory Effects on Sleep

## Inspiratory Muscle Training

### IMT on Endothelial Functional

### IMT on Autonomic Functional

### IMT on Sleep

### IMT on Fatigue and Neurocognitive Dysfunction

## Research Questions and Hypotheses

### Gaps in the Literature

### Aims

# Methods

### Study Design

### Population

### Intervention

### Measures

### Statistical Analysis

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