**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)

Reduced VO2 may be a factor in post-exertional malaise (PEM) (Thomas 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).

### Neurocognitive Dysfunction

Neurocognitive dysfunction, commonly referred to as “brain fog”, is regularly described by PCS patients as one of the most debilitating symptoms (Asadi-Pooya et al., 2023; Jennings et al., 2022; Vyas et al., 2022) (Davis et al., 2021; Nordvig et al., 2023; Orfei et al., 2022; 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 (Davis et al., 2021; Jennings et al., 2022; Nordvig et al., 2023) 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) (Bonner-Jackson et al., 2024; Oh et al., 2024), depression (Jennings et al., 2022) (Bonner-Jackson et al., 2024; Oh et al., 2024), and PSTD (Harenwall et al., 2022; Jennings et al., 2022).

## Respiratory Influence

### Respiratory Effects on Vascular Dysfunction

In healthy populations, aerobic exercise enhances via two distinct mechanisms: anterograde shear and retrograde shear. Increased anterograde shear occurs due to increased pulses of blood emitting from the heart during systole, stimulating endothelial remodeling. In contrast, retrograde shear is not directly affected by cardiac output and instead occurs due to increased respiration. By reducing intrathoracic pressure, the process of inspiration facilitates retrograde shear by drawing blood through the vessels back towards the heart (Tavoian et al., 2023). Unlike anterograde shear – which appears to affect endothelial remodeling through nitric oxide – the effects of oscillatory retrograde shear appears to involve distinct signaling cascades including redox balance, mechanosensitive pathways (kLF2, Nrf2), and endothelial glycocalyx remodeling <CITATION>. Therefore, subjects with intact respiratory systems will reap the dual and concurrent benefits of anterograde and retrograde shear during exercise. In contrast, individuals with compromised ability to reduce intrathoracic pressure via the respiratory musculature may become limited in their potential for vascular adaptations.

### 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 (Ambrosino et al., 2022; Baratto et al., 2021), lower peak minute ventilation (Baratto et al., 2021; Contreras et al., 2023), and elevated VE/VCO2 ratio (Ambrosino et al., 2022; Baratto et al., 2021). 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 Respiratory Function and Dyspnea

# IMT has been shown to improve mechanical properties of the diaphragm including contraction velocity (Benli et al., 2024), excursion (Benli et al., 2024), and thickness (Tanriverdi et al., 2023). These structural adaptations translate into improvements in clinical metrics such as <MIP/PIF/ETC + CITATION>. Most importantly, IMT improves PDIsniff and PESsniff (Langer et al., 2018) (Spiesshoefer et al., 2024)(Spiesshoefer et al., 2024), which is the gold standard of diaphragm strength testing <CITATION>.

# By improving diaphragm function, IMT has a direct beneficial effect on symptoms of dyspnea, and the degree of dyspnea reduction appears directly correlated with the magnitude of enhanced diaphragm functioning (Spiesshoefer et al., 2024). These benefits carryover to reduced dyspnea during physical activity (Langer et al., 2018)(Campos et al., 2018)(Spiesshoefer et al., 2024)

### IMT on Vascular Function

IMT acutely alters shear stress patterns, which is believed to be the proximal stimulus for improvements in FMD. For 1-2 heart beats per load-resisted breath, retrograde shear rate effectively doubles during inspiration and subsequently returns to normal during expiration (Tavoian et al., 2023). Over time, this pulsatile shear stimulus can positively stimulate adaptations for vascular remodeling. Chemical changes indicating improved endothelial function include reduced syndecan-1, angiopoietin-2, and endothelin-1 (Campos et al., 2018).

Consequently, prolonged IMT has been demonstrated to have long-term effects on FMD (Freeberg et al., 2023)(Craighead et al., 2022). For instance, <EXAMPLE>. In some instances this can reduce systolic blood pressure (Freeberg et al., 2023)(Craighead et al., 2022).

### IMT on Exercise Capacity

IMT can improve exercise capacity in tests such as 6MWT <CITATION> (Katayıfçı et al., 2022)(Ammous et al., 2023)(Chen et al., 2023)(Tanriverdi et al., 2023)(Abodonya et al., 2021).

During CPET testing, IMT has been shown to improve VO2 peak (Yáñez-Sepúlveda et al., 2022) (Jimeno-Almazán et al., 2023) (Chen et al., 2023)

The effect of IMT on VO2 appears influenced by degree of respiratory weakness. For instance, an analysis by Trevizan et al. found that IMT improved VO2 peak by 20% in patients with baseline inspiratory muscle weakness compared to only 8% with normal inspiratory strength (Trevizan et al., 2021).

### IMT on Autonomic Function

IMT reduces resting heart rate (Campos et al., 2018).

IMT reduced muscle sympathetic nerve activity (MSNA) by 26% in patients with inspiratory muscle weakness compared to 10% in patients with normal inspiratory strength (Trevizan et al., 2021).

IMT improves multiple metrics of HRV including RMSSD (Tanriverdi et al., 2023)(Edgell et al., 2025), LF/HF (Edgell et al., 2025), pRR50 (Edgell et al., 2025). During exercise, chronotropic exercise improves significantly following an intervention of IMT (Palau et al., 2022).

### IMT on Dyspnea

### IMT on Functional Capacity

IMT improves self-reported functional status (Tanriverdi et al., 2023)(Palau et al., 2022) and physical activity (Katayıfçı et al., 2022) (Jimeno-Almazán et al., 2023).

### IMT on Sleep

IMT improves objective markers of sleep quality such as apnea hypopnea index (AHI) (Azeredo et al., 2022), leading to improvements in subjective reports of sleep quality (Edgell et al., 2025) (Azeredo et al., 2022)

### IMT on Fatigue and Neurocognitive Dysfunction

## Research Questions and Hypotheses

### Gaps in the Literature

### Aims

# Methods

## Study Design

## Population

## Sample Size

A meta-analysis by <AUTHOR> examining IMT on long COVID identified a <EFFECT SIZE> for parameter 1 and a <EFFECT SIZE> for parameter 2 <CITATION>. A power analysis was performed using GPower <VERSION> using the following settings: ANOVA Repeated Measures, within-between interaction F-Test, 5% alpha. With these parameters, it was estimated that <SUBJECTS> would provide 80% power to detect a difference between groups. <SUBJECTS> were recruited to account for potential dropout.

## Intervention

### Inspiratory Muscle Training

#### Intervention Group

IMT was performed using techniques validated in previous clinical studies. Participants in the intervention group performed IMT using a PowerBreathe KH2 (Langer et al., 2018) (Spiesshoefer et al., 2024). Intensity was initially set to 60% of baseline MIP <CITATION>. Resistance was updated weekly to maintain 60% of MIP while accommodating measured strength gains (Bhatnagar et al., 2021; Katayıfçı et al., 2022; Krause-Sorio et al., 2021) (Figueiredo et al., 2018). Participants were instructed to perform 30 breaths twice per day (Ahmadnezhad et al., 2020; Benli et al., 2024; Chung et al., 2021; Schaeffer et al., 2023; Spiesshoefer et al., 2024) on 7 days per week (Ahmadnezhad et al., 2020; Azeredo et al., 2022; Jimeno-Almazán et al., 2023; Langer et al., 2018; Winkelmann et al., 2009). Participants performed IMT remotely and communicated with research staff a minimum of once weekly (Alwohayeb et al., 2018).

#### Control Group

## Measures

### Respiratory

### Vascular

### Autonomic

### Cardiopulmonary Exercise Testing (CPET)

### Dyspnea

### Functional Capacity

### Sleep

### Fatigue

### Neurocognitive Dysfunction

## Statistical Analysis

### Descriptive Statistics

### Group Comparison

### Mediation Analysis

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