# Long COVID

## Pathophysiology

### Exercise

* Lower VE/VCO2 slope (32.1 severe vs 32.9 normal; p = 0.068) (Cherneva et al., 2025)
* No difference in VE/VCO2 (Kersten et al., 2022)
* No difference in VE or VO2 (Samaranayake et al., 2023)
* No difference in VO2 at AT (Kersten et al., 2022)
* No difference in PetCo2
  + (Frizzelli et al., 2022)
* Lower max heart rate
  + (Contreras et al., 2023)
* Lower o2 delivery / utilization
  + Only 2 subjects demonstrated Respiratory Limitation (RL) (Baratto et al., 2021)
  + Lower SaO2 (Baratto et al., 2021)
  + 19.6 versus 17.1 (Baratto et al., 2021)
  + Lower A-VO2 difference with lower peripheral oxygen extraction, (Baratto et al., 2021)
  + Cardiac output
    - No difference in absolute values, but COVID has lower percentage of predicted values (Baratto et al., 2021)
  + No sign of ventilatory impairment, impaired o2 pulse and oxygen uptake capacity (Evers et al., 2022, p. 8)
* Earlier anaerobic threshold
  + Impaired fat metabolism from mitochondria 🡪 higher mean lactate [@deBoerDecreasedFattyAcid]
    - Not associated with COVID symptoms [@deBoerDecreasedFattyAcid]
  + (Frizzelli et al., 2022)
* Low OUES
  + Frizzelli et al., 2022)

### Muscular Strength

* No difference in grip strength
  + (Baker et al., 2023)
* No difference in neuromuscular transmission
  + (Baker et al., 2023)

### Pulmonary

* Lower SpO2 in PCS with fatigue
  + (Baker et al., 2023)

### Cardiac

* No difference in LVEF
  + (Baratto et al., 2021)
* Mildly dilated right ventricle
  + 40 mm vs 35 mm diameter (Baratto et al., 2021)
* Abnormal left or right ventricular strain
  + 1/3 (Baratto et al., 2021)
* Higher cardiac output and PAP at rest, similar total pulmonary resistance (TPR) (Baratto et al., 2021)

### Autonomic Nervous System (ANS)

* No difference in resting heart rate
  + 78 vs 77 (Contreras et al., 2023)
  + (Santos-de-Araújo et al., 2024)
* ANS not associated with dyspnea, fatigue, sleep, or most forms of neurocognitive dysfunction (concentration, memory) (Ladlow et al., 2022)
  + Was associated with poor attention
* ANS is associated with more lactate at rest (Ladlow et al., 2022)
* ANS is associated with higher VE/VCO2 (Ladlow et al., 2022)

## Mediators

### Respiratory

* Respiratory strength and endurance is not associated with VE/VCO2 or Breathing Reserve (Severin, 2022)
* MIP is not lower among OSA vs non-OSA (Rehling et al., 2017)

### Dyspnea

* Improvements in dyspnea are not associated with improvements in fatigue
  + r= 0.122 (insignificant) (Harenwall et al., 2022)
* Dyspnea is associated with reduced VO2 max
  + (Debeaumont et al., 2021)

### Vascular

* Lower EQI (EQI < 2) is NOT associated with:
  + - Sleep (Charfeddine et al., 2021)
* Improvement in endothelial function is NOT associated with improvements in fatigue, dyspnea, brain fog (Charfeddine et al., 2022)
  + Endothelial drug does NOT improve fatigue, dyspnea, brain fog

### Pulmonary

* SpO2 did not correlate with dyspnea severity
  + Long COVID (Paradowska-Nowakowska et al., 2023)

## Symptoms

### Dyspnea

Additionally, dyspnea may also partly be attributed to physiological drive to correct blood gas disturbances due to elevations in arterial CO2 (De Peuter et al., 2004). In the case of PCS, impaired ventilation during activity (Baratto et al., 2021; Contreras et al., 2023) likely compounds these mechanisms, further intensifying symptoms.

### Fatigue

* Improvements in fatigue are associated with improvements in QOL
  + r = -0.371; p < 0.001 (Harenwall et al., 2022)

# Descriptive Statistics

## Age

* Age is associated with:
  + higher rates of fatigue
    - CFQ (Harenwall et al., 2022)
  + reduced activity tolerance
    - Borg scale (Paradowska-Nowakowska et al., 2023)
  + reduced FMD
    - [@riouReducedFlowMediatedDilatation2021]
  + more severe cognitive impairment
    - [@rabaiottiEffectsMultidisciplinaryRehabilitation2023]
    - less risk of cognitive impairment
      * (Bonner-Jackson et al., 2024)
* Age was not associated with:
  + Dyspnea
    - p = 0.372 (Paradowska-Nowakowska et al., 2023)
    - (Craparo et al., 2022)
  + Brain Fog
    - (Craparo et al., 2022)
  + Sensory Disorder

(Craparo et al., 2022)

## Gender

* Females are more likely to experience long COVID
  + [@charfeddineLongCOVID192021]
  + 63.6% (versus 41.1%) (Barbagelata et al., 2022)
  + Higher proportion of females (73.3%) versus controls (59.1%) (Bonner-Jackson et al., 2024)
  + Higher proportion of females (71%) versus controls (58%) (Contreras et al., 2023)
* Females are more likely to experience brain fog
  + (Orfei et al., 2022)
  + (Nordvig et al., 2023)
* Females are more likely to experience dyspnea
  + (Craparo et al., 2022)
* Females are more likely to experience more than 1 long COVID symptom
  + (Craparo et al., 2022)
* Males are more likely to experience brain fog
  + 42.3% of males (u = 6.45) versus 29.1% of females (u = 5.66) [@vyasMildCognitiveImpairment2022]
* Females have better respiratory values than men:
  + FEV1 / FVC
    - (Paradowska-Nowakowska et al., 2023)
* Females have better lung health than men
  + XRAYS/CT
    - (Paradowska-Nowakowska et al., 2023)
* Females have better exercise capacity
  + 6MWT
    - (Paradowska-Nowakowska et al., 2023)
* Females have worse exercise tolerance
  + Borg scale
    - (Paradowska-Nowakowska et al., 2023)
* Females have healthier hearts
  + LVEF
    - (Paradowska-Nowakowska et al., 2023)
* Females are more likely to report the following long COVID symptoms:
  + Myalgia
    - (Paradowska-Nowakowska et al., 2023)
  + Palpitations
    - (Paradowska-Nowakowska et al., 2023)
  + Increased or unstable blood pressure
    - (Paradowska-Nowakowska et al., 2023)
  + Impaired concentration
    - (Paradowska-Nowakowska et al., 2023)
  + Memory deterioration
    - (Paradowska-Nowakowska et al., 2023)
  + Worsened mood
    - (Paradowska-Nowakowska et al., 2023)
  + Sleep disorder
    - (Paradowska-Nowakowska et al., 2023)
  + Hair loss
    - (Paradowska-Nowakowska et al., 2023)
  + Dizziness
    - (Paradowska-Nowakowska et al., 2023)

CPET

* Higher proportion of women in the O2 delivery / utilization group (62.5%) compared to dysfunctional breathing group (46.7%) or the respiratory limitation group (17.9%)

## Ethnicity

* Black race was associated with lower likelihood of cognitive impairment

(Bonner-Jackson et al., 2024)

# IMT

## Outcomes

### Cardiac

* IMT does not improve LVEF
  + (Trevizan et al., 2021)
* IMT does not improve BNP
  + (Trevizan et al., 2021)

### Respiratory

* + Reduced EMGdi / EMG dimax (Langer et al., 2018)
* No change in phrenic nerve conductance
  + [@schaefferEffectsInspiratoryMuscle2023]
* No change in diaphragm EMG [@schaefferEffectsInspiratoryMuscle2023]
* No change in diaphragm thickness
  + (Benli et al., 2024)
  + (Spiesshoefer et al., 2024)
* Dyspnea
* IMT reduces dyspnea
  + Long COVID (McNarry et al., 2022)
  + MRC, TDI (Langer et al., 2018)
  + TDI [@schaefferEffectsInspiratoryMuscle2023]
  + DSI [@abodonyaInspiratoryMuscleTraining2021]
  + Long COVID, improved mmRC (3 to 2) and CRQ dyspnea domain (Spiesshoefer et al., 2024)
  + CHF, mMRC (Tanriverdi et al., 2023)
  + (Katayıfçı et al., 2022)
  + COPD meta-analysis SGRQ, TDI total, mMRC (Ammous et al., 2023)
* IMT does not reduce dyspnea
  + mMRC (Jimeno-Almazán et al., 2023) ## Inhalation
* IMT improves MIP
  + (Katayıfçı et al., 2022)
  + (Alwohayeb et al., 2018)
  + (Freeberg et al., 2023)
  + CKD (Campos et al., 2018)
  + CHF (Trevizan et al., 2021)
  + (Chen et al., 2023)
  + Long COVID (McNarry et al., 2022)
  + (Langer et al., 2018)
  + [@azeredoInspiratoryMuscleTraining2022]
  + (Del Corral et al., 2023), p. 5)
  + mean change: 21.43 meta-analysis [@chenCanInspiratoryMuscle2023]
  + [@schaefferEffectsInspiratoryMuscle2023]
  + CHF (Tanriverdi et al., 2023)
  + Long COVID, +79.4 versus +17.3 (Palau et al., 2022)
* IMT improves inspiratory muscle endurance
  + (Del Corral et al., 2023), p. 5)
  + CHF, ITL (Tanriverdi et al., 2023)
* IMT improves MIP but not above the MCID
  + COPD meta-analysis Mean: 14.57 cmH20 (Ammous et al., 2023)
* IMT improves S-index
  + (Yáñez-Sepúlveda et al., 2022)
* IMT improves SMIP
  + Long COVID (McNarry et al., 2022)
* IMT improves Fatigue Index Time (FIT)
  + Long COVID (McNarry et al., 2022)
* IMT does not improve TLC
  + RMT (Bisconti et al., 2018)
  + Long COVID (Spiesshoefer et al., 2024)

### Oxygen Saturation

* No improvement in SaO2 at nadir or baseline

[@krause-sorioInspiratoryMuscleTraining2021]

* IMT does not improve spO2

CKD (Campos et al., 2018)

* IMT not effective for improving oxygen saturation (spO2)
  + (Langer et al., 2018)

### Autonomic

* No change in LF/HF (Bisconti et al., 2018)
* IMT improves resting heart rate
  + (∆: −2.6 ± 2.9 bpm) (Yáñez-Sepúlveda et al., 2022)
  + CKD (Campos et al., 2018)
  + Long COVID (75 to 68) (Edgell et al., 2025)
* IMT does not improve HRV
  + RMT (Bisconti et al., 2018)

### Exercise Capacity

* No change in dyspnea during exercise
  + [@schaefferEffectsInspiratoryMuscle2023]
* IMT does not improve 6MWT
  + Long COVID, 6MWT, (Spiesshoefer et al., 2024)
* IMT does not improve respiratory rate during CPET
  + CKD (Campos et al., 2018)
* IMT not effective for improving peak workload (W)
  + (Trevizan et al., 2021)
* IMT not effective for improving VO2max / Peak VO2
  + (Trevizan et al., 2021)
* IMT not effective for improving ventilation (Ve)
  + (Langer et al., 2018)
  + [@schaefferEffectsInspiratoryMuscle2023]
* No change in ventilatory efficiency (VE/VCO2)
  + Long COVID (Palau et al., 2022)
* No change in VO2, VE, VE/VO2, RER
  + (Archiza et al., 2018)

### Quality of Life / Functional Capacity

* IMT improves QOL
  + (Katayıfçı et al., 2022)
  + CHF (Trevizan et al., 2021)
  + COPD (Ammous et al., 2023)
  + Long COVID (McNarry et al., 2022)
  + [@abodonyaInspiratoryMuscleTraining2021]
  + CHF, MLHFQ and SF-36 (physical functioning subscale score only)(Tanriverdi et al., 2023)
* IMT does not improve QOL
  + (Del Corral et al., 2023), p. 5)
  + meta-analysis [@chenCanInspiratoryMuscle2023]
  + Long COVID, EQ visual analogue scale (Palau et al., 2022)
* IMT does not improve functional status
  + PCFS (Jimeno-Almazán et al., 2023)
  + Long COVID, Mobility and self-care EQ subdomain (Palau et al., 2022)
* IMT does not increase physical activity
  + (Freeberg et al., 2023)
  + CHF (Tanriverdi et al., 2023)

### Sleep

* No improvement in AHI/RDA
  + [@krause-sorioInspiratoryMuscleTraining2021]

### Fatigue

* IMT does not reduce fatigue
  + ESS [@krause-sorioInspiratoryMuscleTraining2021]
  + FSS, CFS (Jimeno-Almazán et al., 2023)

### Strength

* IMT improves LE strength
  + 60 second sit-to-stand (Del Corral et al., 2023), p. 5)
* IMT does not improve UE strength
  + Grip HHDT (Del Corral et al., 2023), p. 5)
  + Bench 1RM and Grip HHDDT (Jimeno-Almazán et al., 2023)
* IMT does not improve LE strength
  + (Jimeno-Almazán et al., 2023)

### Working Memory

* IMT does not improve working memory
  + (Freeberg et al., 2023) ## Inhibitory Control
* IMT does not improve inhibitory control
  + (Freeberg et al., 2023)

### Attention

* IMT does not improve attention
  + (Freeberg et al., 2023)

### Language

* IMT does not improve vocabulary or oral reading recognition
  + (Freeberg et al., 2023)

### Executive Function

* IMT does not improve executive function
  + (Freeberg et al., 2023)

### Processing Speed

* IMT does not improve processing speed
  + (Freeberg et al., 2023)

### Psychological

* IMT does not improve mental health
  + SF-MH (Jimeno-Almazán et al., 2023)
* IMT does not reduce anxiety
  + GAD7 (Jimeno-Almazán et al., 2023)
* IMT does not reduce depression
  + PHQ9 (Jimeno-Almazán et al., 2023)
* IMT reduces depression and anxiety
  + Long COVID, depression anxiety EQ subdomain (Palau et al., 2022)
* IMT improves mental health
  + PAH -- NHP emotional regulations (Saglam et al., 2015)

### Musculoskeletal

* IMT reduces back pain
  + VAS [@ahmadnezhadInspiratoryMuscleTraining2020]
* IMT reduces “high-threshold” global strategy
  + Decreased RA, erector spinae activity [@ahmadnezhadInspiratoryMuscleTraining2020]
* IMT increases “low-threshold” local strategy
  + Increased TA, multifidus [@ahmadnezhadInspiratoryMuscleTraining2020]
* IMT does not improve balance
  + CHF, (Tanriverdi et al., 2023)
* IMT does not reduce myalgia
  + Long COVID, pain/discomfort EQ subdomain (Palau et al., 2022)

### Vascular

* IMT does not improve PWV
  + No acute change in response to single session (Tavoian et al., 2023)
  + [@Craighead2019InspiratoryMuscleStrength]
* No change in absolute % change, but significant improvement in shear rate (SR) and FMD normalized for shear (%FMD/SR) (Bisconti et al., 2018)
* Increased Diameter peak (Bisconti et al., 2018)
* Blood flow AUC response is 29% lower following RMT training (Bisconti et al., 2018)

## Placebo

justments every week following new MIP assessments. The SHAM group performed the same protocol using 15% of MIP as training load, which is known to elicit negligible training effects (Volianitis et al., 2001).

## Duration

* 12 weeks
  + (Miozzo et al., 2018)
  + (Sadek et al., 2022)
  + improvements initially became apparent at week 3 and continued to increase through week 12 (Winkelmann et al., 2009)
  + (Elshafey & Alsakhawi, 2022)
  + (Dos Santos et al., 2019)
  + [@azeredoInspiratoryMuscleTraining2022]
  + (Palau et al., 2022)
* 4 months
  + (Trevizan et al., 2021)
* 6 months
  + [@schaefferEffectsInspiratoryMuscle2023]
* 4 weeks
  + (Alwohayeb et al., 2018)
  + (Bhatnagar et al., 2021)
* 8 weeks
  + (Del Corral et al., 2023)
  + [@ahmadnezhadInspiratoryMuscleTraining2020]
  + (Langer et al., 2018)
  + (Campos et al., 2018)
  + (Tanriverdi et al., 2023)
* 5 days
  + (Benli et al., 2024)
* 2 weeks
  + [@abodonyaInspiratoryMuscleTraining2021]

Some previous research has found that the benefits of IMT can continue to increase for up to 13 weeks (Krause-Sorio 2021).

# Methods

## Ethics

### Informed Consent

For those who elected to participate in the study, the informed consent document was signed and stored in a locked cabinet accessible to IPL members.

## Analysis

### ANCOVA

Patients with lower baseline MIP are more likely to improve inspiratory strength and functional exercise performance (Gosselink et al., 2011).