Mitochondrial Dysfunction is Associated with Post-Acute Sequelae of COVID-19

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INTRO / BACKGROUND

- Mitochondrial dysfunction has been described in acute severe SARS-CoV2 infection including, altered bioenergetics, reduced oxidative phosphorylation, altered mitochondrial ultrastructure, and decreased proton leak.
- It remains unclear whether the disturbances in mitochondria identified in patients during acute COVID-19 infection are also present in PASC.
- To understand the gap in the current literature on the pathophysiology of PASC and specifically the role that mitochondria may play in PASC, we measured cellular bioenergetics in patients without COVID (COVID-), patients with history of COVID and full recovery (COVID+PASC-) and patients with PASC (COVID+PASC+).

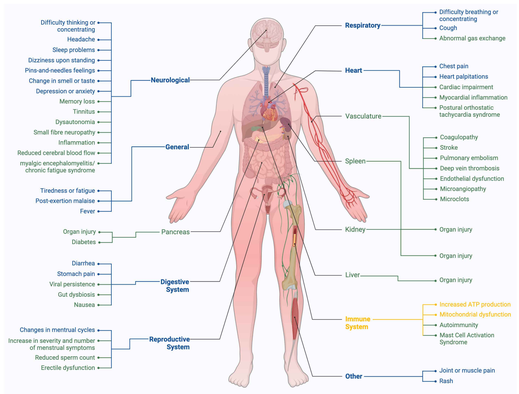


Figure 1. Symptomatology and Pathology of Post-Acute Sequelae of SARS-CoV-2. This figure summarizes the symptoms and pathologies associated with post-acute sequelae of SARS-CoV-2 (PASC) as defined by the CDC (blue), Davis et al., 2023 (green), and found in this study (yellow). Symptoms can vary between persons and can range from mild to severe.

METHODS

Study Design: cross sectional analysis of data from a prospective observational cohort of adult participants at University Hospitals Cleveland Medical Center, Cleveland, Ohio:

- No COVID by history and SARS-CoV2 antibody negative (COVID-),
- With documented prior COVID and full apparent recovery (COVID+ PASC-),
- With prior COVID with PASC symptoms by CDC definition (COVID+PASC+).

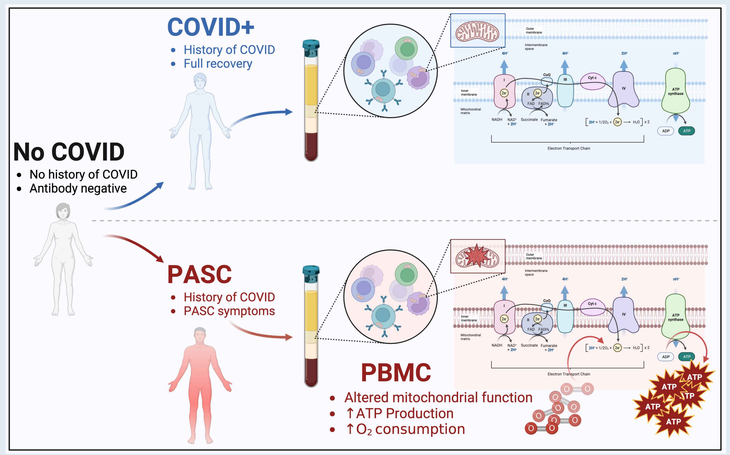
Primary Outcome: Mitochondrial oxygen consumption
Mt oxygen consumption was measured in viable peripheral blood mononuclear cells (PBMCs) using a Seahorse XFe96 to assess the following:

- Basal and maximal respiration
- ATP production
- Proton leak
- Spare respiratory capacity
- Non-mitochondrial respiration

Statistical Analysis:

- Generalized linear regression to compare estimates of respiration between the groups
- Unadjusted odds ratios musing multinomial logistic regression to assess if mitochondrial respiration were associated with PASC

PBMCs from individuals with PASC consume more oxygen and produce more ATP than those from COVID-negative controls. There also is increased PBMC ATP production in PASC compared to COVID+ without PASC



ACKNOWLEDGEMENT

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RESULTS

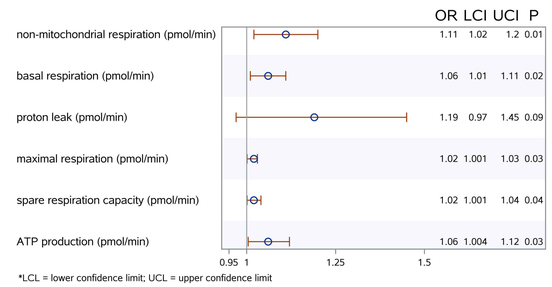
- 59 participants were enrolled; 71% (n=42) had a confirmed COVID-19 diagnosis and among them, 50% (n=21) have PASC symptoms.
- Demographic characteristics are highlighted in Table 1.
- PBMCs Basal respiration, ATP production, maximal respiration, and non-mitochondrial respiration were highest in PASC compared to COVID (p≤0.02, Figure 2).
- There was marginal evidence (p=0.05) of a mean difference in ATP production between COVID+PASC+ and COVID+PASC-, without differences in proton leak (p=0.23) or spare respiration capacity (p=0.07).
- Every unit increase in non-mitochondrial respiration, basal respiration, maximal respiration, and ATP production increased the predicted odds of PASC by 10.99%, 5.6%, 1.6% and 6.2% respectively (Figure 3).

Table 1. Characteristics of Participants by COVID-19 and PASC Status

	No COVID (n=17)	Post-COVID		p-value
		No PASC (n=21)	PASC (n=21)	
	n (%) or median (IQR)/mean ± std			
Demographics				
Age (years)	47 ± 19	49 ± 14	46 ± 12	0.89
Female Sex	12 (71)	14 (67)	15 (71)	0.94
Non-white Race	7 (41)	6 (29)	7 (33)	0.72
Hypertension at Baseline (Yes)	2 (12)	5 (24)	6 (29)	0.04
Diabetes at Baseline (Yes)	0	2 (10)	3 (14)	0.06
Post-acute Symptoms				
Number of days since COVID diagnosis	- -	193(54, 288)	224 (147, 453)	0.27
Total Number of Symptoms	- -	- -	9 (5, 13)	- -
1 to 6	- -	- -	8 (38)	- -
>=7	- -	- -	13 (62)	- -

whiskers represent interquartile range

Association of Mitochondrial Respiration on PASC
Unadjusted Odds Ratio(OR), 95% Confidence Intervals(CIs), and P-value(P)



*LCL = lower confidence limit; UCL = upper confidence limit

OR: Adjusted odds ratio, 95% CI (lower confidence interval= LCI; upper confidence interval= UCI), p value

CONCLUSION

- PASC participants' PBMCs consumed more oxygen than those without COVID and produced more ATP than both those without COVID and patients with a history of COVID without PASC.
- The high oxygen consumption, ATP production, and high maximal respiration in PBMCs suggest an increase in oxidative stress, or a compensatory mechanism for underlying mitochondrial dysfunction.
- Future studies are needed to investigate mitochondrial dysfunction in PASC, taking into consideration the different phenotypes, so that individualized and tailored therapies can be developed.

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