

Excerpt from **Long COVID and the Autonomic Nervous System** article published in [MDPI](#)

Introduction

COVID-19 is documented to adversely affect the autonomic nervous system. In many patients, the lingering effect on the autonomic nervous system results in what has been termed long COVID. Long COVID is well documented to involve the autonomic nervous system.

Autonomic Dysfunction in Long COVID

Autonomic dysfunctions may be peripheral or central. In central cases, autonomic dysfunctions may be related to microglial hyperactivation inside the brainstem autonomic centers. Microglial hyperactivation is associated with PE. Autonomic dysfunctions may also be highly influenced by psychological factors.

Parasympathetic Excess and Sympathetic Withdrawal in Long COVID

In our findings, Long COVID is largely characterized by parasympathetic excess and sympathetic withdrawal, both potentially contributing to hypoperfusion of the brain and all structures above and around the heart. Pre-COVID-19 infection, patients presented to the clinics with more sympathetic withdrawal (45.7%) than parasympathetic excess (27.0%). Post-COVID-19 infection, these patients presented with that ratio reversed (36.2% and 46.7%, respectively). The etiology of this is not well known; however, parasympathetic excess may be more prominent post-COVID-19, due to an over-active immune system, which the parasympathetics help to control and coordinate and leads to parasympathetic excess.

Role of the Parasympathetic Nervous System in Immune Response

Given that the parasympathetic nervous system controls and coordinates the immune system, severe infections lead to excessive and prolonged parasympathetic activation in response to challenges or stressors (known as parasympathetic excess), which exacerbates autonomic and cardiovascular dysfunctions.

Orthostatic Dysfunction and COVID-19

A common, and perhaps first cause of autonomic dysfunction, due to mitochondrial dysfunction and associated oxidative stress, is orthostatic dysfunction, resulting in poor cardiac and cerebral perfusions (and, of course, all the structures around and above the heart). Orthostatic dysfunction is caused by poor vasoconstriction due to alpha-adrenergic (sympathetic) dysfunction, known as sympathetic withdrawal. Poor perfusion and dysfunction are exacerbated by the effect of COVID-19 on the lungs. Both parasympathetic excess and sympathetic withdrawal are separate and treatable dysfunctions.

Pharmaceutical Treatment of Autonomic Dysfunction

As in this study, parasympathetic excess was treated, pharmaceutically, with anti-cholinergics (e.g., Nortriptyline, see the Methods Section) and sympathetic withdrawal was treated, pharmaceutically, with oral vasoactives (e.g., Midodrine, see the Methods Section). Our findings demonstrate an initial worsening of autonomic dysfunction and symptoms associated with COVID-19 infection, and then, with autonomic treatment, these dysfunctions and symptoms may again be relieved.

Sympathovagal Balance and Post-COVID-19 Syndrome

Traditionally, upon COVID-19 infection, there is a marked increase in the resting sympathetic activity and a decrease in anti-inflammatory resting parasympathetic activity, causing a high (resting) sympathovagal balance in all patients. However, in post-COVID-19 syndrome patients, after 12 weeks or more, our data shows that there is a significant percentage of patients that develop a parasympathetic dominance as indicated by the low (resting) sympathovagal balance. This is also indicative of increasing and prolonged parasympathetic activity.

Protective Role and Complications of Parasympathetic Activation

Parasympathetic activation is meant to be protective; including, since the parasympathetics are anti-inflammatory. However, prolonged and increased parasympathetic activity, especially in response to stressors, seems to exaggerate sympathetic inflammatory activity. Within this cohort, and anecdotally with the vast majority of our patients, anti-cholinergic therapy relieves parasympathetic excess. Further studies are required to elaborate whether anti-cholinergic therapy may relieve post-COVID-19 symptoms.

Symptoms of Long COVID Linked to Oxidative Stress and P&S Dysfunction

All symptoms of long COVID may be explained by oxidative stress and P&S dysfunction. For example, P&S dysfunction leading to orthostatic dysfunction underlies poor cerebral (including all structures above the heart) perfusion, which causes fatigue, brain-fog, cognitive and memory difficulties, sleep difficulties, and other depression-like symptoms, including “coat-hanger” pain, headaches and migraines; cranial nerve dysfunctions, including visual and auditory effects (including tinnitus), taste and smell deficits, and facial sensations due to trigeminal nerve dysfunction.

Blood Pressure and Cerebral Perfusion Compensatory Mechanisms

P&S dysfunction may also increase BP (and may eventually lead to hypertension) as a compensatory mechanism to promote cerebral perfusion. Further decreases in cerebral perfusion may lead to “adrenaline storms”, which cycle anxiety-like symptoms, including shortness of breath and palpitations which may cause chest pressure or chest pain. The effects of sympathetic withdrawal and orthostatic dysfunction are exacerbated by parasympathetic excess, which may limit or decrease the heart rate and blood pressure, reducing cerebral perfusion. The decrease in BP is also associated with excessive vasodilation from parasympathetic excess.

Prolonged Parasympathetic Excess in Long COVID

If the parasympathetics increase in response to a stress (known as parasympathetic excess), the result is a secondary sympathetic excess. Our findings of prolonged parasympathetic excess in long-COVID patients appears to prolong sympathetic excess responses causing more and chronic symptoms, suggesting that this may be a mechanism contributing to long-COVID syndrome.

Conclusion and Need for Further Research

Pharmaceutical therapy for P&S dysfunction (anti-cholinergics for parasympathetic excess and oral vasoactives for sympathetic withdrawal) needs to be very low to prevent additional symptoms, thereby exacerbating P&S dysfunction. From Table 3, COVID-19 significantly increases autonomic dysfunctions and the associated symptoms, and autonomic therapy significantly reduces autonomic dysfunctions and the associated symptoms. Further studies are needed, including blinded, controlled studies.

Long COVID and the Autonomic Nervous System: The Journey from Dysautonomia to Therapeutic Neuro-Modulation through the Retrospective Analysis of 152 Patients Joseph Colombo 1,* , Michael I. Weintraub 2,* , Ramona Munoz 1 , Ashish Verma 1 , Ghufran Ahmad 1 , Karolina Kaczmarek 1 , Luis Santos 3 and Nicholas L. DePace 1 1 Franklin Cardiovascular, Autonomic Dysfunction and POTS Center, Sicklerville, NJ 08081,USA;

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