Long-COVID and the Autonomic Nervous System: The journey from Dysautonomia to Therapeutic Neuro-Modulation, Analysis of 152 Patient Retrospectives

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Abstract

Introduction: The severity and prevalence Post-Acute COVID-19 Sequela (PACS) or Long-COVID Syndrome (Long-COVID) should not be a surprise. All Long-COVID symptoms may be explained by Oxidative Stress and Parasympathetic and Sympathetic (P&S) dysfunction. This is a retrospective, hypothesis generating, outcomes study.

Methods: From two suburban practices in the northeastern United States, 152 Long-COVID patients were (1) P&S tested (P&S Monitor 4.0; Physio PS, Inc., Atlanta, GA) prior to COVID-19 infection due to other causes of Autonomic dysfunction, with (2) a pre-COVID follow-up P&S test after autonomic therapy, then the patients (3) were infected by COVID-19, then (4) the patients were P&S tested within three months of surviving COVID-19 infection with Long-COVID symptoms, and (5) were post-COVID, follow-up P&S tested, again, after autonomic therapy. All patients completed Autonomic Questionnaires with each test. This cohort included 88 Females (57.8%), with an average age of 47.0 years (ranging from 14 to 79 years), and an average BMI of 26.9 #/in².

Results: More pre-COVID patients presented with Sympathetic Withdrawal than Parasympathetic Excess. Post-COVID, these patients presented with that ratio reversed and, on average, 49.9% more autonomic symptoms than they did pre-COVID.

Discussion: Both Parasympathetic Excess and Sympathetic Withdrawal are separate and treatable autonomic dysfunctions and autonomic treatment significantly reduces the prevalence of autonomic symptoms.

Conclusion: SARS-CoV-2, via its oxidative stress, can lead to P&S dysfunction, which in turn affects the control and coordination of all systems throughout the whole body and may explain all symptoms of Long-COVID syndrome. Autonomic therapy leads to positive outcomes and patient quality of life may be restored.

Keywords: Long-COVID; Parasympathetic; Sympathetic; Autonomic Dysfunction; Autonomic Therapy; Outcomes
Introduction

The severity and prevalence of Post-Acute COVID-19 Sequela (PACS) or Long-COVID Syndrome (Long-COVID) should not be a surprise. SARS-CoV-2 targets diverse organs and tissues after entry into the human body. Long-COVID syndrome is defined as persistent symptoms beyond 12 weeks after acute COVID infection [1,2,3,4]. Viruses have two main targets upon infection: 1) the hosts’ DNA to replicate, and 2) the hosts’ Mitochondria for the energy to do so. The attack on the Mitochondria causes Oxidative Stress. Given that nerve cells, including brain cells, and heart muscle cells contain significantly more Mitochondria than other cells in the body, it is to be expected that they will be the most affected by Oxidative Stress. Results of Mitochondrial dysfunction includes primarily Autonomic (including both Parasympathetic and Sympathetic [P&S]) dysfunction and Cardiovascular dysfunction [5]. Arguably the first symptom of P&S dysfunction is Orthostatic dysfunction [6,7,8]. Orthostatic dysfunction is a significant contributor to poor cardiac and cerebral perfusion (and of course all structures around and above the heart). Autonomic dysfunction is also induced as a result of the severity of the infection [9].

Of course COVID-19, also scars the lungs reducing their ability to exchange oxygen, exacerbating the poor perfusion and resulting dysfunctions. The initial respiratory compromise due to COVID-19 virus on the medullary respiratory control centers (including the pre-Bötzinger complex) [10,11,12] may be so dramatic that P&S symptoms and signs are often overlooked or misunderstood. Respiratory pacing from the pre-Bötzinger complex involves Vagus nerve afferents, among other brainstem structures, and feedback from COVID-damaged lung, Aortic and Carotid chemo-, baro- and vagal receptors and Medullary chemoreceptors also involve P&S nerves [10,13]. Brainstem cardiorespiratory centers (e.g., Nucleus Tractus Solitarius, Dorsal Vagal Motor Nucleus, and Nucleus Ambiguus) are also implicated in COVID-19 infection [14]. Furthermore, Sympathetic involvement in cytokine storms [15,16,17,18] and the angiotensin system [19,20], and Parasympathetic involvement in immune function [21,22,23], provides further evidence of P&S compromise in COVID-19 infection. Any resulting damage to these nerves further implicate P&S dysfunction in Long-COVID syndrome.

All Long-COVID symptoms [24] may be explained by Oxidative Stress and P&S dysfunction. This study presents data from autonomic dysfunction patients who were (1) P&S tested prior to COVID-19 infection due to other causes of Autonomic dysfunction, with (2) a follow-up P&S test after autonomic therapy, then (3) were infected by COVID-19, then (4) the patients were P&S tested within three months of surviving COVID-19 infection with Long-COVID symptoms, and (5) were follow-up P&S tested, again, after autonomic therapy.

- All Long-COVID symptoms may be explained by Oxidative Stress and P&S dysfunction.
- Long-COVID is largely characterized by Parasympathetic Excess and Alpha-Sympathetic Withdrawal upon head-up, postural change.
- Anti-cholinergic therapy may relieve post-COVID symptoms associated with Parasympathetic Excess.

Methods

From two suburban practices in the northeastern United States (Sicklerville, NJ and Briarcliff Manor, NY): a cardiovascular and autonomic dysfunction clinic and a neurology clinic (respectively), with patients drawn from around the world, 152 Long-COVID patients were tested according to the five steps listed at the end of the Introduction. This cohort included 88 Females (57.8%), with an average age of 47.0 years (ranging from 14 to 79 years), and an average BMI of 26.9 #/in2. All patients were tested with P&S Monitoring (P&S Monitor 4.0; Physio PS, Inc., Atlanta, GA) and completed a 28 symptom questionnaire (Table 1). This is a retrospective, observational, hypothesis generating, outcomes study. All patients permitted their data to be included in this large population study and patient data were maintained according to HIPPA guidelines.
P&S Monitoring collects EKG, Respiratory Activity and BP during four challenges: (1) rest (baseline), (2) deep breathing (0.1 Hz, a Parasympathetic challenge), (3) short Valsalva maneuvers (< 15 seconds, as a Sympathetic challenge), and (4) head-up postural change (stand, which is equivalent to tilt [1]. Stand is both an Orthostatic challenge and a measure of the coordination between the P&S branches. With spectral analyses these data are analyzed and independent and simultaneous P&S activity is measured throughout the clinical study [8]. Normal and abnormal P&S response plots are depicted in Figures 1 through 5, including in order 1) a normal resting baseline response (Figure 1), 2) a normal stand or upright posture response (Figure 2), 3) an abnormal alpha-Sympathetic Withdrawal response (upon standing) indicating Orthostatic dysfunction (Figure 3), 4) an abnormal Parasympathetic Excess response (upon standing) indicating a Vagal Excess (Figure 4), and 5) an abnormal Parasympathetic Excess with Hyperadrenergic response (upon standing) indicating Vasovagal Syncope (Figure 5) [8].

**Table 1**: 28 Symptom Autonomic Dysfunction Questionnaire

<table>
<thead>
<tr>
<th>Lightheaded Fatigue</th>
<th>Chest pain, palpitations</th>
<th>Short of breath</th>
<th>Fainting and near fainting</th>
<th>Difficulty standing</th>
<th>Sweat too much, too little</th>
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</thead>
<tbody>
<tr>
<td>Brain Fog or Mental cloudiness</td>
<td>Difficulty findings words</td>
<td>Short term memory loss</td>
<td>Insomnia, Sleep Difficulty</td>
<td>Depression, anxiety</td>
<td>Tension headaches</td>
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<tr>
<td>Chronic Pain</td>
<td>Coat hanger pain in neck &amp; shoulders</td>
<td>Pins and needs in arms/legs</td>
<td>Numbness in hands and feet</td>
<td>Hypermobility joints, joints pop out</td>
<td>Nausea, vomiting</td>
</tr>
<tr>
<td>Sensory: hypersensitive to light, sound, motion, touch</td>
<td>Sensory deficits: vision, hearing, taste, smell</td>
<td>Cold hands or feet</td>
<td>Ringing in ears</td>
<td>Does hot or cold weather bother you</td>
<td>Hands or Feet turn colors (Red, White or Blue) in cold temperatures</td>
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**Figure 1**: “Normal at Rest” An example Resting (Baseline) P&S Response Plot. The gray area depicts the normal response region. The purple highlighted areas depict the definitions of Advanced Autonomic Dysfunction (AAD, light purple), Diabetic Autonomic Neuropathy (DAN, also light purple) and Cardiovascular Autonomic Neuropathy (CAN, dark purple). AAD and DAN indicate morbidity risk and CAN indicates mortality risk. Risk is stratified by Sympathovagal Balance. The space between the two outer diagonal lines defines normal Sympathovagal Balance (“LFa/RFa”), regardless of resting autonomic state. Normal Sympathovagal Balance normalizes morbidity and mortality risks. Above and to the left of the upper diagonal line indicates low Sympathovagal Balance which is a resting Parasympathetic Excess. Below and to the right of the lower diagonal line indicates high Sympathovagal Balance which is a resting Sympathetic Excess.
Figure 2: “Normal upon Standing” An example normal Stand P&S Response Plot. Active standing is equivalent to positive, head-up, tilt [25]. The point ‘A’ is the patient’s resting, baseline response and the point ‘F’ is the patient’s stand response. In the normal Stand response, the Parasympathetics (the blue line) first decrease and then the (alpha-)Sympathetics (the red line) increases. [8]

P&S Monitoring differs from all other autonomic monitors in that it is uniquely capable of measuring the two individual autonomic branches independently and simultaneously without assumption and approximation [2,3,4,5]. P&S monitoring permits follow-up testing, and includes indications for Peripheral Autonomic Neuropathy (including Small C-Fiber Disease) as well as P&S dysfunctions (including autonomic neuropathies) not detected by typical autonomic monitors, including: Sympathetic Withdrawal (an alpha-adrenergic insufficiency upon assuming a head-up posture, associated with Orthostatic dysfunction) [6] and Parasympathetic Excess (an excessive cholinergic response to a stress, as modeled by Valsalva challenge or upon assuming a head-up posture, associated with Vagal over-reactions) [7].
Sympathetic Withdrawal (see Figure 3) and Parasympathetic Excess (see Figure 4) are two of the P&S dysfunctions typically demonstrated by Long-COVID patients. Others included are: 1) Sympathetic Excess with up-right posture (a beta-adrenergic response associated with Syncope and pre-Syncopal symptoms. See Figure 5), 2) low and 3) high Sympathovagal Balance (a measure of the ratio of Sympathetic to Parasympathetic activity at rest, see Figure 1), 4) low resting Sympathetic or Parasympathetic activity at rest associated with Advanced Autonomic Dysfunction or Diabetic Autonomic Neuropathy if a diabetic (see Figure 1), and 5) very-low resting Parasympathetic activity at rest associated with Cardiovascular Autonomic Neuropathy. (see Figure 1.)

Based on their P&S test results, patients were prescribed therapy which typically included 2.5mg, tid, Midodrine (ProAmatine, an alpha-adrenergic antagonist) with up to 600mg, tid, Alpha-Lipoic Acid (an antioxidant selective for nerves [8,9,10,11,12,13]) for Sympathetic and Orthostatic dysfunction (after ruling out vascular causes) and 10mg, qd, Nortriptyline (as a low-dose anticholinergic) with up to 40 minutes low-and-slow exercise [14] for Parasympathetic dysfunction. Pearson Correlation and Student's T-Test Statistics are based on SPSS v. 20.
**Figure 4**: "Vagal Excitation" An example abnormal Stand P&S Response Plot depicting Parasympathetic Excess. The point 'A' is the patient's resting, baseline response and the point 'F' is the patient's stand response. Here the Sympathetic response is normal (see Figure 2), but the Parasympathetic response increases abnormally, indicating Vagal or Parasympathetic Excess, associated with difficult to control BP, blood glucose, hormone level, or weight, difficult to describe pain syndromes (including CRPS), unexplained arrhythmia (palpitations) or seizure, temperature dysregulation (both response to heat or cold and sweat responses), and symptoms of depression or anxiety, ADD/ADHD, fatigue, exercise intolerance, sex dysfunction, sleep or GI disturbance, lightheadedness, cognitive dysfunction or "brain fog", and frequent headache or migraine. Parasympathetic Excess and Sympathetic Withdrawal may occur concurrently, including Parasympathetic Excess may mask Sympathetic Withdrawal. [8]
Results

In general, patients reported poor health. All patients first presented (pre-COVID) with lightheadedness (100%), due to (1) pre-Syncope (28.3%) or Syncope (2.6%), (2) Orthostatic dysfunction, including Postural Orthostatic Tachycardia Syndrome (POTS, 8.6%) and Orthostatic Intolerance or Orthostatic Hypotension (36.8%), or (3) excessive Vagal symptoms (27.0%). Approximately a quarter (25.7%) of the cohort first presented with Anxiety-like symptoms, including palpitations and shortness of breath. Over a third (36.9%) of the cohort reported fatigue, nearly half (46.9%) reported generalized pain, including headache and migraine, and over half of whom (25.7% of the total cohort) are diagnosed with Ehlers-Danlos Syndrome – Hypermobility (see Table 2). The prevalence of the autonomic dysfunctions are listed in Table 3. Sympathetic Withdrawal is the most prevalent autonomic dysfunction pre-COVID and Parasympathetic Excess is the most prevalent post-COVID.

Figure 5: “Vagal Excitation + Hyperadrenergic” An example abnormal Stand P&S Response Plot depicting Parasympathetic Excess with Sympathetic Excess. The point 'A' is the patient's resting, baseline response and the point 'F' is the patient's stand response. Here the Parasympathetic response is abnormal (see Figure 2), and the Sympathetic response increases too much, exceeding the normal area. The combination indicates Vasovagal Syncope. The Parasympathetic Excess is the Vagal component, and the Sympathetic Excess (Hyperadrenergic response) indicates the nervous system’s response to Syncope and the accompanying poor cerebral perfusion. [8]
Upon initial presentation (pre-COVID), these autonomic dysfunction patients presented with an average of 2.34 of the 7 P&S dysfunctions. With fewer than 9 months of therapy the pre-COVID patients were found with an average of 0.95 of the 7 P&S dysfunctions (p<0.001). Post-COVID, these patients demonstrated an average 3.67 of the 7 P&S dysfunctions (p=0.004). With fewer than 6 months of therapy the post-COVID patients were found with an average of 1.63 of the 7 P&S dysfunctions (p=0.003).

Pre-COVID baseline these patients complained of an average of 9.74 of the 28 symptoms. Upon pre-COVID follow-up these patients complained of 6.25 symptoms (p=0.009). Post-COVID these patients complained of an average of 14.6 of the 28 symptoms (p<0.001). Upon post-COVID follow-up these patients complained of an average of 7.44 symptoms (p=0.004). COVID-19 infection added to the number of (56.8% more) autonomic dysfunctions and increased the number of (49.9% more) associated symptoms. All patients reported improved outcomes, which is evidenced by the fewer P&S dysfunctions and fewer symptoms reported upon follow-up.

From Table 3, acute COVID infection also reversed the order of the top two autonomic dysfunctions from Sympathetic Withdrawal being more predominant pre-COVID to Parasympathetic Excess being more predominant post-COVID. Abnormal Sympathovagal Balance also become more significant. Those who also demonstrated low Sympathovagal Balance (resting Vagal excess) also reported more significant symptoms of depression/anxiety and fatigue. Those who demonstrated high Sympathovagal Balance (resting Sympathetic excess) also reported more significant symptoms of pain and hypertension.

**Discussion**

COVID-19 is documented to adversely affect the autonomic nervous system [1]. In many, the lingering effect on the autonomic nervous system results in what has been termed Long-COVID [2]. Long-COVID is well documented to involved the autonomic nervous system [3,4,5]. In our findings, Long-COVID is largely characterized by Parasympathetic Excess and Sympathetic Withdrawal. Pre-COVID patients presented to clinic with more Sympathetic Withdrawal (45.7%) than Parasympathetic Excess (27.0%). Post-COVID, 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 due to the over-active immune system which the Parasympathetics help to control and coordinate and leads to Parasympathetic Excess. Both Parasympathetic Excess and Sympathetic Withdrawal are separate and treatable dysfunctions. As in this study, Parasympathetic Excess was treated with anti-cholinergics (e.g., Nortriptyline, see Methods) [31] and Sympathetic Withdrawal was treated with oral vasoactives (e.g., Midodrine, see Methods) [30]. Given that the Parasympathetic nervous system controls and coordinates the Immune System, severe infections lead to exces-

<table>
<thead>
<tr>
<th>Cohort</th>
<th>No</th>
<th>No. Female</th>
<th>Ave. Age</th>
<th>Ave. BMI</th>
<th>LH</th>
<th>Fatigue</th>
<th>Anxiety</th>
<th>Headache, Migraine</th>
<th>EDSh</th>
</tr>
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<tr>
<td></td>
<td>152</td>
<td>88 (57.8)</td>
<td>47.0 yrs</td>
<td>26.9 lbs/ft²</td>
<td>152 (100)</td>
<td>56 (36.9)</td>
<td>39 (25.7)</td>
<td>71 (46.9)</td>
<td>39 (25.7)</td>
</tr>
</tbody>
</table>

Ave. Average; BMI Body Mass Index; EDSh Ehlers Danlos Syndrome/Hypermobility; LH Lightheadedness; No. Number

**Table 2**: Patient Demographics upon first presentation

<table>
<thead>
<tr>
<th></th>
<th>SW</th>
<th>PE</th>
<th>SE</th>
<th>Low SB</th>
<th>Hi SB</th>
<th>AAD</th>
<th>CAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-COVID</td>
<td>45.4</td>
<td>27.0</td>
<td>12.5</td>
<td>15.1</td>
<td>27.0</td>
<td>17.1</td>
<td>5.3</td>
</tr>
<tr>
<td>Post-COVID</td>
<td>36.2</td>
<td>46.7</td>
<td>28.9</td>
<td>38.2</td>
<td>45.4</td>
<td>20.4</td>
<td>6.6</td>
</tr>
</tbody>
</table>

**Table 3**: Percentage prevalence of the autonomic dysfunctions in Long-COVID patients. See text for details and abbreviations.
sive and prolonged Parasympathetic activation (aka., Parasympathetic Excess or Parasympathetic Excess) [44] which exacerbates Autonomic and Cardiovascular dysfunction. A common, and perhaps first cause of Autonomic dysfunction due to Mitochondrial dysfunction and associated Oxidative Stress, is Orthostatic dysfunction [6,7] resulting in poor cardiac and cerebral perfusion (and of course all structures around and above the heart). Orthostatic dysfunction is caused by poor vasoconstriction due to alpha-adrenergic (Sympathetic) dysfunction, known as Sympathetic Withdrawal [8]. Poor perfusion and dysfunction are exacerbated by the effect of COVID-19 on the lungs.

Our findings demonstrate an initial worsening of autonomic dysfunction and symptoms associated with COVID infection and then with autonomic treatment these dysfunctions and symptoms may again be relieved. Traditionally upon COVID infection there is a marked increase in resting Sympathetic activity and a decrease in anti-inflammatory resting Parasympathetic activity [6], causing high (resting) Sympathovagal Balance in all patients. However, in post-COVID syndrome patients after 12 weeks or more, our data shows that there is a significant percentage of patients that develop a Parasympathetic dominance with low (resting) Sympathovagal Balance indicative of increasing and prolonged Parasympathetic activity. This is meant to be protective, since the Parasympathetics are anti-inflammatory; however, prolonged increased Parasympathetic activity exaggerates Sympathetic inflammatory activity. Further studies to elaborate whether anti-cholinergic therapy may relieve post-COVID symptoms are needed.

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; “coat-hanger” pain, headache and migraine; Cranial Nerve dysfunction including visual and auditory effects (including Tinnitus), taste and smell deficits, and facial sensations due to Trigeminal nerve dysfunction; and increases in BP (and eventually hypertension) as a compensatory mechanism to promote cerebral perfusion. Further decreases in cerebral perfusion leads “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 heart rate and blood pressure reducing cerebral perfusion. The decrease in BP is also associated with excessive vasodilation from the Parasympathetic Excess.

The Sympathetic nervous system is the reactionary nervous system and responds based on the thresholds set by the Parasympathetic nervous system. Normally, in response to a stress (whether healthy or unhealthy), the Parasympathetics (which respond faster than the Sympathetics [26]) first decrease then the Sympathetics respond. The decrease in Parasympathetic activity potentiates and facilitates (including minimizes) Sympathetic responses. However, if the Parasympathetics increase in response to a stress (known as Parasympathetic Excess), the result is a secondary Sympathetic Excess [8]. It is well known that Sympathetic Excess may lead to (1) high heart rates (including palpitations), (2) high BP (including difficult to control BP or labile hypertension), (3) excessive histaminergic responses (including Mast Cell Activation Syndrome), (4) excessive inflammatory responses (including various Rheumatological disorders), (5) amplified pain responses (including generalized pain syndromes and Small C-Fiber Disease causing abnormal sweating, poor temperature control and responses to heat and cold, and poor wound healing), (6) exaggerated mental responses (including panic attacks and Anxiety-like symptoms), etc. All of these Sympathetic responses are meant to be short-lived, acute, minimalistic responses. Parasympathetic Excess exaggerates the Sympathetic response, causing Sympathetic Excess, which amplifies the responses, and prolonged Parasympathetic Excess prolongs these responses causing more and chronic symptoms.

A first line therapy for Sympathetic Withdrawal and Parasympathetic Excess is antioxidants. Exercise, Alpha-Lipoic Acid, and Co-Q10 are arguably the most powerful antioxidants. These therapies are natural and often employed due to the fact that many patients present with histories of pharmaceuticals in high dose, limiting their tolerance to these medications, even in very-low doses. Pharmaceutical therapy for P&S dysfunction (anti-cholinergics for Parasympathetic Excess and oral vasoactive for Sympathetic Withdrawal) needs to be very low to prevent additional symptoms thereby exacerbating P&S dysfunction. Adding pharmaceutical therapy to the natural therapies help to accelerate the relief of symptoms. P&S therapy in general requires low-and-slow administration to gently establish and maintain P&S balance; requiring up to 24 months depending on duration and severity of the cause of P&S dysfunction. If prolonged or maintenance therapy is required, the natural remedies are typically considered. In both cases, pre- and post-COVID infection, the very low-dose pharmaceutical, supplement and lifestyle modification therapies employed significantly
reduced the number of autonomic symptoms and dysfunctions over a six to nine-month period. Autonomic dysfunctions were reduced by 59.4%, pre- and 55.6% post-COVID, and autonomic symptoms were reduced by 35.8%, pre- and 49.0% post-COVID; as compared with pre- and post-COVID infection baselines.

**Conclusion**

The current body of evidence suggests that the SARS-CoV-2 can affect the nervous system in previously unexpected ways [41-45]. Mitochondrial damage, especially in the P&S nervous systems, in turn affects the control and coordination of all systems throughout the whole body and may explain all symptoms of Long-COVID syndrome. The association of Anxiety, Postural Orthostatic Tachycardia Syndrome (POTS) and Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME), with Long-COVID is interesting because all are also characterized by P&S dysfunction. However, to diagnose these conditions, including Long-COVID, independent and simultaneous (direct) measures of P&S activity are required; for the assumptions and approximations required by other autonomic tests are typically not appropriate for these patients. These direct measures are needed because both autonomic branches are involved in Long-COVID in different ways and must be treated separately, and may be treated at the same time. Therapy is low-and-slow and patient expectations must be properly established for optimum compliance. Follow-up testing is needed to help with compliance and ensure that therapy is properly titrated to the individual patient. Based on all of this, positive outcomes are realized and patient quality of life may be restored. While this study serially followed patients with underlying autonomic dysfunction pre- and post-COVID, future studies should assess the effects of autonomic function on normal subjects pre and post COVID.
References


