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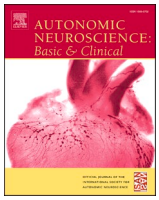

Review

Preparing for the long-haul: Autonomic complications of COVID-19

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ABSTRACT

As global numbers of COVID-19 grow, chronic neurological symptoms, including those of autonomic dysfunction, are being reported with increasing frequency. Mounting evidence suggests that many patients experience chronic and sometimes debilitating symptoms long after their acute infectious period, leading to the new diagnostic category of post-acute COVID syndrome. Many symptoms of post-acute COVID syndrome appear autonomic in nature, suggesting that autonomic impairment may play a central role in the underlying pathophysiology. In this review, we discuss the autonomic symptoms and manifestations of post-acute COVID syndrome, potential mechanisms involved, and future directions for a better understanding of this novel condition.

1. Introduction

COVID-19 is an ongoing pandemic of unprecedented scale. The causative virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can lead to a broad spectrum of manifestations, from asymptomatic infection to severe respiratory illness and death. Autonomic symptoms of acute infection are common and are being described with increasing frequency. While most patients have mild symptoms and recover within several weeks, more than 50% are left with ongoing symptoms several months later (Huang et al., 2021), many of which appear autonomic in nature. This chronic form of the illness is still being defined and has been referred to by many names including "post-COVID syndrome," "post-COVID-19 syndrome," "post-acute COVID syndrome (PACS)," "post-acute sequalae of SARS-COV-2 infection (PASC)," "long-COVID" and "long-haul COVID." For the purposes of this article, we will refer to this disorder as PACS. Many of the symptoms of PACS are like those experienced by patients with chronic autonomic dysfunction, and cases of postural orthostatic tachycardia syndrome (POTS) developing after the acute para-infectious period of COVID-19 are being reported with increasing frequency. In this perspective, we will review chronic autonomic complications of COVID-19, potential pathophysiological mechanisms of autonomic dysfunction, and future considerations in exploring the link between COVID-19 and autonomic impairment.

2. Chronic autonomic complications of prior coronavirus pandemics: SARS and MERS

Chronic fatigue and to a lesser extent autonomic impairment have been described as sequelae of severe acute respiratory syndrome (SARS), the coronavirus pandemic of 2002-2004 that resulted in 8422 cases and 916 deaths (11% mortality, Chan-Yeung and Xu, 2003). A large number of patients with SARS experienced prolonged fatigue and exercise intolerance long after the acute phase of the illness, with studies reporting that 40% of patients (67% female) still had chronic fatigue nearly two years after infection (Lam et al., 2009). In a study of 22 SARS survivors who were unable to return to work after a mean of 20 months, most patients reported chronic pain, persistent fatigue, myalgias, psychological distress, and disturbed sleep, all of which contributed to their disability (Moldofsky and Patcai, 2011). Eighty-six percent of this cohort were female and nearly all were health-care workers. The authors emphasized that these symptoms were similar to those experienced by patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), a post-viral syndrome known to have a strong association with autonomic impairment (Freeman and Komaroff, 1997; Newton et al., 2007).

Studies utilizing autonomic reflex testing are limited in post-SARS syndrome. One study of 14 patients (85% female) demonstrated an abnormal 30:15 ratio on active stand testing in 4/14 (29%) patients at six months post-infection, with three reporting orthostatic intolerance (Lau et al., 2005). No patient had evidence of orthostatic hypotension

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(OH);exaggerated postural tachycardia was not mentioned. Nerve conduction testing was normal in all patients, and one patient had absent bilateral lower limb sympathetic skin responses suggestive of small fiber neuropathy. All patients reported chronic fatigue.

Persistent tachycardia appears to be a common symptom in post-SARS syndrome. In a study of 121 SARS patients (64% female) admitted to the hospital, tachycardia was the most common cardiovascular condition, and nearly 40% of patients had persistent tachycardia three weeks after discharge (Yu et al., 2006).

Middle East respiratory syndrome virus (MERS) was a much smaller coronavirus pandemic in 2012 that resulted in 2468 cases and 851 deaths (34% mortality; WHO and Annon, 2020a). As a result, literature on chronic symptoms in survivors is limited. While neurological complications including sensory neuropathy have been reported in the para-infectious period (Kim et al., 2017), to our knowledge there are no reports of autonomic impairment following MERS.

Acute respiratory distress syndrome (ARDS), a common complication of SARS, MERS, and COVID-19, has itself been correlated with chronic limitations in functioning regardless of underlying etiology. In a cohort of 117 ARDS survivors (64% female) who had been treated in the intensive care unit (ICU), all patients continued to have functional limitations one year after discharge with the majority of patients at only 66% of predicted exercise capacity (Herridge et al., 2003). Exercise intolerance was independent of pulmonary function testing results in this cohort.

2.1. Chronic autonomic complications of COVID-19

Compared to SARS and MERS, the pandemic of COVID-19 is of a dramatically larger scale. At the time of this revision on June 12, 2021, there are nearly 175 million cases and over 3.7 million deaths worldwide (2.2% mortality rate), a case count at this moment 70,874 times greater than SARS (WHO and Annon, 2020b). The prevalence of chronic symptoms in COVID-19 survivors is incompletely understood, however initial reports have suggested that up to 50% of patients continue to experience symptoms that persist well after the para-infectious period (Huang et al., 2021). If this is indeed the case, the numbers of those with PACS-related disability will be sizeable.

PACS has been used to describe an array of symptoms that persist long after initial SARS-CoV-2 infection (Greenhalgh et al., 2020). While the duration of symptoms required to diagnose PACS has not been clearly defined at the time of this writing, most reports have detailed symptoms extending beyond 12 weeks. The United Kingdom's National Institute for Health and Care Excellence (NICE) has defined "post-COVID-19 syndrome" as symptoms that persist for >12 weeks and "long-COVID" as both ongoing symptomatic COVID-19 (symptoms lasting 4–12 weeks) and post-COVID-19 syndrome (symptoms >12 weeks: National Institute for Health and Care Excellence and Annon, 2020.). While the US National Institutes of Health (NIH) has recently used the term post-acute sequalae of SARS-CoV-2 (PASC), the duration of illness required for this diagnosis has not been specified. Regardless, PACS appears to be a multisystem illness, the most common systemic symptoms being fatigue, headaches, and cognitive impairment ("brain fog"), as well as other symptoms suggestive of autonomic dysfunction such as orthostatic intolerance, palpitations, and gastrointestinal dysfunction (Huang et al., 2021; López-León et al., 2021: Table 1)

In April to June of 2020 the Center for Disease Control (CDC) conducted a multistate telephone survey of 274 non-hospitalized COVID-19 survivors in the US and found that approximately 1/3 (52% female) had not returned to their usual state of health two to three weeks after infection, including 20% of younger patients with no prior medical conditions (Tenforde et al., 2020). Fatigue (71%), cough (61%), and headache (61%) were the most frequently reported symptoms. In a study of 143 hospitalized COVID-19 survivors in Italy with more severe disease (53% female), 87% still had symptoms at 60 days with 53% reporting fatigue, 43% reporting difficulty breathing, and 22% reporting chest pain (Carfì et al., 2020). Another study of 767 COVID-19 survivors in Italy, 88% of whom had been hospitalized, reported that 51% remained symptomatic at a median of 105 days post-infection with fatigue and exertional dyspnea being the most common symptoms (Venturelli et al., 2021). Females (32% of cohort) reported more symptoms than males and were twice as likely to report fatigue. In a study of 120 hospitalized COVID-19 patients in Paris (37% female) surveyed a mean of 111 days after admission (37% female), 55% of patients reported fatigue, 42% dyspnea, and 34% memory loss (Garrigues et al., 2020). A preprint of a study of 84 COVID-19 survivors in New York found that 92% of patients (sex of patients not reported) still had fatigue, 74% loss of concentration/memory, and 64% dizziness with symptoms persisting a mean of 151 days (range 54-255 days: Tabacof et al., 2020). A study of 1733 individuals (48% female) in the Wuhan province of China, evaluated six months after hospital discharge for COVID-19 infection, reported that 76% of individuals continued to experience at least one persistent symptom with "fatigue or muscle weakness" (63%) and sleep difficulties (26%) among the most common (Huang et al., 2021). Other symptoms included palpitations (9%), dizziness (6%), diarrhea or vomiting (5%), chest pain (5%), skin rash (3%), and headache (2%); these symptoms are also common in patients with autonomic disorders. Approximately one-quarter of these patients had an abnormal six-minute walk test. Patients who were more severely ill during their initial infection were more likely to report persistent symptoms, have impaired pulmonary diffusion capacity on pulmonary function testing, and have abnormal chest computed tomography (CT). Finally a study of Swiss military recruits (13% female) demonstrated that 19% of those infected with SARS-CoV-2 had a reduction of >10% maximum oxygen uptake (VO2 max) on exercise testing performed at a median of 45 days post-infection regardless of the severity of initial symptoms (Crameri et al., 2020).

Table 1
Symptoms commonly reported in post-acute COVID syndrome.[a]

Fatigue
Headache
Cognitive impairment ("brain fog")
Dyspnea
Orthostatic intolerance[a]
Palpitations/tachycardia[a]
Temperature intolerance[a]
Labile blood pressure[a]
New-onset hypertension[a]
Gastrointestinal symptoms (e.g., abdominal pain, bloating, nausea)[a]
Symptoms of mast cell activation syndrome (e.g., pruritis, urticaria, flushing, angioedema, wheezing, gastrointestinal symptoms, tachycardia, labile blood pressure)

[a] Symptoms suggestive of autonomic dysfunction.

Reports from COVID-19 survivors themselves have been invaluable in raising awareness and understanding PACS, originally termed "long-haul COVID" by survivors.[1] Several "long-haul COVID" support groups, consisting of hundreds of thousands of COVID survivors from around the world formed on social media, and have conducted their own patient-experience surveys. One survey created by the Body Politic COVID-19 support group targeted those who continued to experience symptoms for at least two weeks after initial infection (Assaf et al., 2020). Of the 640 respondents, the majority were never hospitalized for COVID-19. Sixty-three percent were between the ages of 30 and 49, and 77%

[1] We would like to recognize Amy Watson, a COVID survivor from Oregon who coined the phrase "Long Haul COVID" on April 29, 2020, as she was thinking of a name for the Facebook support group she created to help COVID survivors with prolonged symptoms connect with each other. The phrase was inspired by the trucker hat she was wearing, and has been used extensively by fellow patients, media outlets, government officials, and the scientific community. More than 10,000 "long haulers" have found each other though Ms. Watson's group to date.

were female. Among the most common symptoms were those often reported by patients with autonomic disorders including fatigue, tachycardia, lightheadedness, difficulty concentrating ("brain fog"), insomnia, headache, gastrointestinal upset, and nausea. Many respondents reported no pre-existing conditions and 90% had not fully recovered 40 days after the onset of their illness. Sixty percent of this population reported pre-existing conditions such as asthma, which the authors suggested might prolong recovery time.

Another patient advocacy group, the COVID-19 Longhauler Advocacy Project, surveyed 1200 individuals who had been ill for five weeks or longer after SARS-CoV-2 infection (range 5-54 weeks; Bishof, 2020). Most respondents developed COVID-19 in March of 2020; the survey was administered in October of 2020. Many reported mild to moderate symptoms during the period of acute infection. Respondents, who were advised not to include any pre-existing medical conditions, reported the development of new neurological (67%), pulmonary (53%), gastrointestinal (51%), cardiac (49%), and sensory (27%) problems. Notably, 34% reported new diagnoses of autonomic dysfunction, and 18% reported new diagnoses of autoimmune disease, however these diagnoses were not substantiated by medical records.

More recently, the Patient-Led Research Collaborative, which grew out of the Body Politic COVID-19 support group, reported data on a follow-up survey of 3762 individuals across 56 countries with either suspected or confirmed COVID-19 who reported symptoms >28 days after initial infection (Davis et al., 2020). Most respondents were female (79%) and white (85%). The most frequent symptoms reported after six months were fatigue (78%), post-exertional malaise (72%), and cognitive dysfunction (55%). The authors found that for those who recovered within 90 days of symptom onset, the average number of symptoms peaked at week two, while for those who did not recover by 90 days, the average number of symptoms peaked at month two after symptom onset.

In a systematic review of 15 studies addressing persisting symptoms in COVID-19, the most commonly reported symptoms were fatigue (58%), headache (44%), "attention disorder" (27%), hair loss (25%), and dyspnea (24%, López-León et al., 2021). The authors also reported symptoms commonly seen in those with autonomic disorders, including "post-activity polypnea" (21%), sweating abnormalities (17%), nausea/vomiting (16%), chest pains/discomfort (16%), "resting heart rate increase" (11%), sleep disorders (11%), flushing (5%), and dizziness (3%). A new diagnosis of hypertension was reported in 1% of patients. It should be acknowledged that not all studies reviewed assessed all symptom domains, and that prevalence estimates are in some cases limited by small sample sizes.

Other researchers have described persistent autonomic symptoms over 100 days after initial symptom onset in COVID-19 survivors, including autonomic symptoms such as night sweats, tachycardia upon mild exercise or standing, temperature dysregulation, constipation, loose stools, and vasomotor instability, however some of these reports are anecdotal (Nath and Billioux, 2020). A group in the Paris-Ile-de-France area described a subset of younger female patients ("around 40 years-old" in a 4:1 female: male ratio), with persistent fatigue, myalgias, subjective fevers, shortness of breath, tachycardia, chest tightness, anxiety, and headaches (Davido et al., 2020), a presentation strikingly similar to that of a typical patient with POTS. The authors hypothesized that these symptoms were consistent with autonomic dysfunction and should be considered as such, proposing a theory of microangiopathy and endothelial injury in susceptible patients as the underlying mechanism. These later descriptive reports should be viewed as preliminary only. At this stage in our understanding of PACS, it is unclear whether the symptoms reported are reflective of a sustained systemic inflammatory response, damage to autonomic pathways, or other mechanisms.

More recently there have been several case reports focusing more specifically on autonomic dysfunction in PACS (Johansson et al., 2021; Kanjwal et al., 2020; Miglis et al., 2020; Novak, 2020). Almost all cases were females, with prominent autonomic symptoms that emerged several weeks after acute infection (Table 2). It should be noted that not all patients had SARS-CoV-2 infection confirmed via real time-polymerase chain reaction (RT-PCR) or antibody testing, for the most part due to limited availability during the early stages of the pandemic. Common symptoms include orthostatic intolerance, exercise intolerance, palpitations, fatigue, and cognitive impairment. Several patients had features of a hyperadrenergic state (Johansson et al., 2021; Miglis et al., 2020), and symptoms of mast cell activation were not uncommon (Johansson et al., 2021; Miglis et al., 2020). In those that had standardized autonomic cardiovascular reflex testing performed, the majority had an exaggerated postural tachycardia, acknowledging that some referral bias is present in the reporting of these data. Most patients were treated symptomatically with a combination of fluid, salt, rate control agents, and volume expanders, with variable outcomes. One patient experienced resolution of many PACS symptoms with intravenous immunoglobulin (IVIG), including neuropathic pain, brain fog, urinary incontinence, and blurred vision and partial improvement in headaches and chronic fatigue, (Novak, 2020), raising the possibility of an autoimmune mechanism. However, it is difficult to confirm from a single case report whether the patient improved due to the passage of time or due to an actual immunomodulatory effect. Further research is needed to better understand potential autoimmune mechanisms in PACS and treatment approaches.

While POTS appears thus far to be the most common autonomic phenotype among PACS patients, OH and neurally-mediated syncope should also be considered. In a three-month follow-up study of 135 patients with confirmed COVID-19 in Austria, "orthostatic hypotension with vasovagal syncope due to autonomic dysregulation" was seen in 1% (Rass et al., 2021). While it is presumed based on the description that these two patients had both orthostatic hypotension and vasovagal syncope, it is unclear how these diagnoses were made and what role deconditioning may have played, as one patient was admitted to the ICU. The median age of patients in this study was 56 years and most were male (61%). Other neurological diagnoses made at three months that were not present prior to SARS-CoV-2 infection included polyneuro/myopathy (13%) with one patient presenting with Guillain-Barré syndrome (1%), mild encephalopathy (2%), parkinsonism (1%), and ischemic stroke (1%).

In a prospective study of 40 COVID-19 survivors (90% female), with a median follow-up of 166.5 days (range 154.5–179 days), the authors reported no signs of cardiovascular autonomic dysfunction on reflex testing as measured by Ewing's autonomic battery with beat-to-beat blood pressure (BP) and heart rate (HR) measurement during deep breathing, Valsalva, cold pressor testing, and a five-minute stand test (Townsend et al., 2021). Fourteen of the 20 fatigued patients (70%) reported palpitations, dizziness or lightheadedness, or chest discomfort on active stand, while these symptoms were reported by none of the non-fatigued patients. The authors reported normal autonomic testing in all 40 patients, however, HR and BP analyses were not reported beyond three minutes, thus limiting sensitivity for diagnoses of POTS, delayed OH, or neurally-mediated syncope. Half of the study population had no fatigue and had returned to work, however it is unclear if this half of patients had any post-viral symptoms at all. All patients in this cohort had mild to moderate initial disease. Furthermore, patients who had received any medication that could impact cardiovascular findings, such as beta blockers, were excluded, as were patients who could not complete the five-minute stand test and other study procedures. Future research will explore whether these findings can be confirmed in larger cohorts of patients with well-defined PACS.

In another study from Germany, 42 PACS patients presenting with persistent moderate to severe fatigue six months after mostly mild SARS-CoV-2 infections were assessed with the Composite Autonomic Symptom Score-31 (COMPASS-31, Kedor et al., 2021). A majority had COMPASS-31 scores suggestive of moderate ($n = 21$) or severe ($n = 11$) autonomic dysfunction.

The extent of central and peripheral nervous system involvement in COVID-19 remains to be determined; the same applies to the autonomic

Table 2
Case reports of post-acute COVID autonomic dysfunction.

Authors and patient demographics	Timing of symptoms and confirmation of diagnosis	ANS testing and diagnosis	Symptoms	Treatment and response
Author: Miglis et al., 2020 Patient: 26-year-old female	URI symptoms 7 days prior to ANS symptom onset; Nasal RT-PCR and IgG positive	ANS testing: HUT showed a sustained HR increase of up to 65 bpm with episodic BP surges Diagnosis: POTS	OI, tachycardia, chest pain, shortness of breath, fatigue, exercise intolerance, insomnia, diarrhea, restlessness	Treatment: - Increased fluid and salt intake - Compression garments - Propranolol, clonidine Response: - Resolution of symptoms after eight months
Author: Kanjwal et al., 2020 Patient: 36-year-old female	Fever, fatigue and shortness of breath 3-4 weeks prior to onset of ANS symptoms; IgG positive	ANS Testing: HUT showed a HR increase of 41 bpm without BP fall Diagnosis: POTS	OI, fatigue, headache, chest pains, palpitations	Treatment: - Increased salt and water intake - Ivabradine Response: - Improvement in orthostatic symptoms and tachycardia
Author: Novak, 2020 Patient: 64-year-old female	Cough, dyspnea and headaches 3 weeks prior to onset of ANS symptoms; Nasal RT-PCR positive	ANS Testing: Not performed Diagnosis: Exacerbation of baseline OCHOS and small fiber neuropathy	Burning sensation in feet and hands, twitching and vibration in her face, blurred vision, brain fog, headaches, chronic fatigue, OI, urinary incontinence	Treatment: - IVIG Response: - Resolved leg pain, brain fog, urinary problems, blurred vision - Headaches and chronic fatigue improved by about 50%
Author: Johansson et al., 2021 Patient: 42-year-old female	Flu like symptoms with loss of smell and taste 1 and 3 months prior to onset; IgG "borderline positive"	ANS Testing: HUT showed a HR increase of 50 bpm with initial OH, hyperadrenergic response on Valsalva maneuver Diagnosis: POTS	OI, tachycardia, palpitations, fatigue, heat, and exercise intolerance	Treatment - Increased fluid intake - Compression stockings - Beta-blockers and Ivabradine Response - Beta-blockers worsened orthostatic intolerance - Ivabradine resulted in substantial improvement
Author Johansson et al., 2021 Patient: 28-year-old female	Fever, dyspnea, chest pain, lightheadedness and headache that persistent and progressed; Nasal RT-PCR positive and IgG positive	ANS Testing: Active standing test showed a HR increase of 53 bpm without BP fall, HUT showed symptomatic sinus tachycardia >130 bpm without BP fall Diagnosis: POTS	Chest pain, fatigue, vertigo, headache, OI. After several weeks, she developed gastrointestinal symptoms, itching, and orbital edema. Concern for MCAS.	Treatment - Increased fluid and salt intake - Compression stockings - Propranolol - H1 and H2 antihistamines (for mast cell activation syndrome) Response Remains highly symptomatic and is on sick leave
Author: Johansson et al., 2021 Patient: 37-year-old man	Sore throat, fever, fatigue, muscle weakness, dry cough, and palpitations that persisted; IgG negative on multiple occasions	ANS Testing: Active standing test showed a HR increase of 44 bpm without BP fall Diagnosis: POTS	Fatigue, muscle weakness, insomnia, palpitations, "brain fog" with trouble concentrating. Also developed nausea, orbital edema and gastrointestinal symptoms. Concern for MCAS.	Treatment - Increased fluid and salt intake - Compression stockings - Propranolol and pyridostigmine - H1 and H2 antihistamines (for mast cell activation syndrome) Response Remains highly symptomatic and on sick leave
Author: Dani et al., 2021 Patient: 26-year-old female	Gastrointestinal symptoms 5 days prior to symptoms;Suspected viral illness	ANS Testing: Active standing test with postural HR 121–150 bpm without BP fall. Diagnosis: POTS	Palpitations on standing, dyspnea, fatigue	Not specified

(*continued on next page*)

Table 2 (*continued*)

Authors and patient demographics	Timing of symptoms and confirmation of diagnosis	ANS testing and diagnosis	Symptoms	Treatment and response
Author: Dani et al., 2021 Patient: 43-year-old female	Upper respiratory tract symptoms 1 month previously; Suspected COVID-19	ANS Testing: Active standing test with postural HR 86–106 bpm, ambulatory BP monitor with diurnal sinus tachycardia with HR 68–159 bpm Diagnosis: POTS	Palpitations, fatigue Breathlessness	Not specified
Author: Dani et al., 2021 Patient 50-year-old female	Chesty cough March 2020; Suspected COVID-19	ANS Testing: Active standing test with postural BP 136/48 to 115/91 mmHg, postural HR 48–60 bpm Diagnosis: OI	Palpitations, chest pain	Not specified
Author: Dani et al., 2021 Patient: 30-year-old female	Flu-like symptoms March 2020; Confirmed COVID-19	HUT with BP from 106/69 to 72/52 mmHg and HR increase from 67 to 99 bpm Diagnosis: OI, "reactive tachycardia"	Aches, dizziness, diarrhea and palpitations	Not specified
Author: Dani et al., 2021 Patient: 50-year-old female	Suspected COVID-19 infection March 2020	ANS Testing: HUT with postural BP drop of 17 mmHg and HR rise to 132 bpm after 24 min Diagnosis: OI with a predisposition to vasovagal presyncope	Recurrent presyncopal episodes, fatigue, panic attacks	Not specified
Author: Dani et al., 2021 Patient: 44-year-old female	URI symptoms for 5 weeks in March 2020; Suspected COVID-19	ANS Testing: none Diagnosis: OI	OI, fatigue, irritable bowel symptoms, anxiety	Not specified

ANS = autonomic nervous system, URI = upper respiratory infection, OI = orthostatic intolerance, HUT = head-up tilt, POTS = postural tachycardia syndrome, OCHOS = orthostatic cerebral hypoperfusion syndrome.

nervous system. Reports of autonomic dysfunction with Guillain-Barré syndrome in patients with COVID-19 have been reported during the acute para-infectious period, suggesting the possibility of immune-mediated autonomic neuropathy (Ghosh et al., 2020; Su et al., 2020; Toscano et al., 2020). In a study assessing sudomotor function using electrochemical skin conductance (ESC) in 50 patients (32% female) with a history of COVID-19, 48% of whom had been hospitalized, abnormal ESC was seen in 26% of patients (Hinduja et al., 2021). In those patients with abnormal ESC, autonomic symptoms were common and included "rapid heartbeat" (77%), "bloating or belching" (39%), and "low blood pressure" (39%). While suggestive of small fiber autonomic impairment, these data require confirmation with other validated techniques of sudomotor function such as quantitative sudomotor axon reflex (QSART) testing and skin biopsy.

3. Potential mechanisms of autonomic impairment in post-acute COVID syndrome

3.1. Tissue injury

Given that angiotensin converting enzyme-2 (ACE2) receptors are heavily expressed in endothelial cells lining many tissues throughout the human body—including those intricately involved in autonomic function such as endothelial cells in large and small arteries and veins, respiratory epithelium, enterocytes of all parts of the small intestine, proximal tubule of the kidney, and basal cell layer of the epidermis (Hamming et al., 2004)—chronic complications arising from direct injury inflicted during the parainfectious period of COVID-19 is quite possible. There have been numerous reports of prolonged respiratory dysfunction, including interstitial lung disease, abnormal chest radiographs and CT imaging, and impaired gas exchange in patients who survived SARS, MERS, and now COVID-19 (Das et al., 2017; Fraser, 2020; Hui et al., 2005). These patients often report fatigue, exercise intolerance, cognitive impairment and reduced exercise capacity. Thus, some degree of autonomic symptomatology might be due to persisting cardiopulmonary injury. In support of this theory, a study of 100 COVID-19 patients demonstrated that 78% demonstrated signs of ongoing inflammation on cardiac MRI at a median of 71 days after initial infection (Puntmann et al., 2020). Others have noted positive correlations between the severity of SARS-CoV-2 infection and signs of chronic lung injury, with considerable numbers of moderate to severely ill patients exhibiting pulmonary diffusion and chest CT abnormalities six months after symptom onset (Huang et al., 2021). The most common finding on chest CT in these studies was pulmonary interstitial changes, similar to radiographic changes seen in SARS survivors (Xie et al., 2005).

The possibility of renal impairment should also be considered. Epithelial cells of the proximal renal tubule contain ACE2 receptors that could facilitate SARS-CoV-2 entry, leading to cytotoxicity and inflammatory cell infiltration. Furthermore, SARS-CoV-2 downregulates ACE2 receptors after cellular entry, leading to excess production of angiotensin II, which may in turn lead to vasoconstriction, increased vascular permeability, inflammation, and fibrosis (Rossi et al., 2020). A review of 1000 hospitalized COVID-19 patients reported that 34% developed acute kidney injury and 13.8% of these required dialysis (Argenziano et al., 2020). In our experience, new-onset hypertension in PACS in not uncommon, and while longitudinal outcome data are lacking, this presentation should be considered in the evaluation of patients with PACS.

The hypercoagulable state of COVID-19 may also contribute to chronic pulmonary emboli. Indeed, small pulmonary emboli have been visualized in patients with persistently elevated D-dimers several months after their initial infection (Venturelli et al., 2021), which may contribute to exertional dyspnea.

Finally, direct infection of neural tissues is possible. SARS-CoV-2 ribonucleic acid (RNA) has been isolated from the olfactory bulb,

branches of the trigeminal nerve (including conjunctiva and cornea), the cerebellum, respiratory and cardiovascular nuclei in the medulla, and the carotid artery wall (Meinhardt et al., 2021), the latter two sites being of utmost importance in baroreflex function. Additionally, ACE2 receptors have recently been identified in the dorsal root ganglia, another potential pathway into the peripheral nervous system (Shiers et al., 2020). It is plausible to consider that such receptors may also be expressed on autonomic ganglia given the close regulatory relationship between ACE2 and the autonomic nervous system, however this remains to be documented.

3.2. Immune-mediated mechanisms

Viral infections are commonly reported triggers of autonomic dysfunction and there are many viral pathogens that have been implicated (Carod-Artal, 2018). Prior research suggests that 41% of patients with POTS report symptom onset after a viral prodrome (Thieben et al., 2007), raising suspicion of immune-mediated mechanisms. Recent evidence documenting high titers of adrenergic and other autoantibodies to G-protein-coupled receptors in POTS may support this theory (Fedorowski et al., 2017; Gunning et al., 2019; Wang et al., 2012; Ruzieh et al., 2017), however further studies are needed to confirm causation. Such autoantibodies have also been reported in viral myocarditis and Chagas cardiomyopathy (Rodeles et al., 2016). Rapidly evolving research is identifying a wide array of extracelluar autoantibodies in individuals with COVID-19 (Wang et al., 2020). The role of autoimmunity in PACS is thus yet to be defined and is deserving of future research, especially as it relates to autonomic disorders of orthostatic intolerance such as POTS, OH, and neurally-mediated syncope. The interaction of the autonomic nervous system with aspects of immune, endocrine, and allergic function are incredibly complex and while conceptual frameworks have been provided (Goldstein, 2020a, 2020b), mechanistic studies in patients with PACS-related autonomic dysfunction will ultimately be necessary to explore these associations.

Mast cell activation syndrome (MCAS) resulting in cytokine storms and hyperinflammation has also been implicated in chronic post-COVID illness (Afrin et al., 2020). Support for this theory comes from the observation that much of the systemic inflammation seen in COVID-19 is like that seen in those with MCAS. Furthermore, preliminary findings suggest that some drugs with activity against mast cells may be beneficial in those with COVID-19. Curiously, prior in vitro research demonstrates that adrenergic receptor autoantibodies cause mast cells in cardiomyocyte tissue to mature faster and degranulate more readily (Okruhlicova et al., 2007). Symptoms of MCAS are also reported in those with PACS, many of whom had no prior history of allergic symptoms, though reports are limited at the moment.

3.3. Baroreflex impairment

While we were only able to identify one publication detailing OH in PACS (two patients out of a cohort of 137, both of whom had been hospitalized due to severity of para-infectious symptoms, Rass et al., 2021), this complication may be more common than reported due to the lack of routine orthostatic BP measurements in both inpatient and outpatient practice. In addition, syncope can be a presenting sign of COVID-19. In one study, syncope was reported in 35 out of 411 (8.5%) patients early in the disease course (Canetta et al., 2020), however, another publication reported rates of syncope closer to 1% (Rass et al., 2021). The syncope seen in patients with COVID-19 infection is presumed to be neurally-mediated and possibly related to viral invasion or disruption of baroreflex pathways in the carotid artery or the nucleus tractus solitarious of the medullawhich contains ACE2 receptors, though mechanistic studies have not been performed. We and others have noted a predilection for a hyperadrenergic presentation in these patients with exaggerated BP responses on Valsalva maneuver, orthostatic hypertension along with exaggerated orthostatic postural tachycardia, and labile BPs, suggestive of an exaggerated baroreflex response (Johansson et al., 2021; Miglis et al., 2020). This is deserving of future research with inclusion of patients across various age groups to gather a more comprehensive understanding of not only orthostatic HR but also BP complications of SARS-CoV-2 infection.

3.4. Gender physiology

Based on available data, PACS appears to affect females more than males and especially so in autonomic cardiovascular domains such as orthostatic intolerance and inappropriate tachycardia. The reasons for this are unclear, however there are several possibilities. Most females have up to 1/3 less skeletal muscle mass than males (Janssen et al., 2000) and hence a less vigorous “muscle pump” on standing, have smaller hearts (Prabhavathi et al., 2014), and are more prone to pelvic venous pooling (Summers et al., 2010), all which may be significantly exacerbated if deconditioning is introduced, further worsening orthostatic intolerance.

Additionally, there are sex-based differences in innate and adaptive immune responses, which impact the immunological response to pathogens (Klein and Flanagan, 2016). Females are also more prone to autoimmune disease, with an approximately 4:1 ratio compared to men by some estimates (Angum et al., 2020). The role of autoimmunity in PACS will thus be critical in the understanding of post-COVID autonomic dysfunction and how this impacts gender predilection.

3.5. Deconditioning

Cardiovascular deconditioning is a potential consequence of COVID-19, as periods of prolonged bedrest can lead to resting tachycardia, reduced exercise capacity, and a predisposition to orthostatic intolerance (Hasser and Moffitt, 2001). Cardiovascular deconditioning leading to persistent tachycardia has been described after SARS (Yu et al., 2006) and may also play a role in PACS and its association with orthostatic intolerance. The role of deconditioning in POTS continues to be vigorously debated. While low stroke volume and decreased cardiac mass have been proposed as evidence of deconditioning in POTS (Parsaik et al., 2012), other authors suggest this may be the consequence of low ventricular filling pressures (Oldham et al., 2016), however this finding is inconsistent with the high filling pressures typically seen in deconditioned patients (Blitshteyn and Fries, 2016). Finally, deconditioning alone does not explain the many other symptoms present in POTS and also seen in PACS, including cognitive impairment, gastrointestinal upset, sleep disturbances, and neuropathic pain. In many POTS patients, reconditioning programs can lead to improvement, but rarely to complete resolution of symptoms. This has also been our experience in patients with PACS.

Further studies evaluating VO2 max, ventricular filling pressure and other parameters of exercise testing are needed to better understand the extent of deconditioning in PACS patients. Until we understand the role of deconditioning in the progression of disease, it will be difficult to ascertain which autonomic symptoms are caused or worsened by the presence of deconditioning.

4. Future directions

The first cases of COVID-19 were reported in Asia in December 2019 and the first cases in North America and Europe in January 2020, with many surges occurring in March-April 2020 and then again in December 2020-March 2021. We are in the early stages of our understanding of COVID-19 and in even earlier stages of understanding PACS: its prevalence, extent of disease, and effect on the autonomic nervous system. What cannot be denied is that there will be a wave of patients to come; if COVID-19 is the earthquake, PACS may well be the tsunami.

The first challenge will involve defining the post-viral illness: cardinal features, duration of disease, inclusion and exclusion criteria. As

this definition is being shaped, well-characterized patient registries will be critical for future research. We and others hope to recruit such patients for further study including testing of autonomic cardiovascular reflexes, serological markers including those of allergic and immune function, skin biopsy and other sudomotor tests of small nerve fiber function, tests of mitochondrial function, cardiac and neuroimaging studies. Such studies should be collaborative, with the establishment of open access data registries across centers and harmonization of data sets. Funding sources should emphasize both acute and long-term care for COVID-19 patients; centers of excellence for post-COVID care should be prioritized at academic institutions to lead the way in multidisciplinary rehabilitative care. We are encouraged by the recent allocation of $1.15 billion by the US Congress to the study of the prolonged effects of COVID-19 with aim towards these goals, and we encourage federal agencies to leverage the expertise of centers that have studied post-viral syndromes such as POTS and ME/CFS for decades, to build upon existing knowledge and accelerate the pace of research on PACS.

While additional data are needed, we suspect that early diagnosis and treatment of autonomic and other sequelae may improve long-term outcomes, reducing the severity of chronic illness in PACS patients. While guidelines are still being shaped, we recommend that all patients with PACS are queried for symptoms of autonomic dysfunction (Table 1). Standardized, easy to complete autonomic questionnaires such as the COMPASS-31(Sletten et al., 2012) can be considered to both screen for autonomic dysfunction and track symptom changes over time. Patients with symptoms of orthostatic intolerance such as lightheadedness, fatigue, cognitive impairment, or orthostatic headaches should undergo a 10-min orthostatic stand test or head-up tilt table test to evaluate for disorders of orthostatic intolerance such as POTS and OH. If patients meet criteria for these conditions, existing management guidelines may aid clinicians unfamiliar with these diagnoses (Figueroa et al., 2010; Fu and Levine, 2018; Miller and Raj, 2018). While exercise therapy has been recommended by some societies in early treatment guidelines for PACS(National Institute for Health and Care Excellence and Annon, 2020), caution is warranted until more evidence emerges. In our experience, many PACS patients experience post-exertional malaise (PEM) after physical activity, like what is experienced by those with ME/CFS, therefore graded physical reconditioning should be tailored to the individual and considered once cardiovascular and other autonomic symptoms are stabilized. Future research will also need to prioritize mechanisms involved in chronic fatigue of those with PACS, how it relates to the diagnosis of post-COVID ME/CFS, and if patients who are diagnosed with this condition are distinct from those diagnosed with post-COVID POTS or other post-COVID autonomic disorders.

Prior to COVID-19, individuals with autonomic disorders frequently waited months to years to gain access to the few autonomic specialty clinics that exist in the US; there are even fewer clinics per capita in other countries. As the volume of PACS patients with autonomic sequelae far exceeds the capacities of existing autonomic clinics, government agencies, professional societies, medical schools and community hospitals should endeavor to train clinicians on how to recognize PACS and related autonomic dysfunction, how to initiate standard treatments for post-viral autonomic syndromes, and when to refer such patients to post-COVID care clinics, autonomic clinics, or other specialty clinics.

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Declaration of competing interest

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