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COMPENDIUM ON COVID-19 AND CARDIOVASCULAR DISEASE

A Post-Pandemic Enigma: The Cardiovascular Impact of Post-Acute Sequelae of SARS-CoV-2

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ABSTRACT: COVID-19 has become the first modern-day pandemic of historic proportion, affecting >600 million individuals worldwide and causing >6.5 million deaths. While acute infection has had devastating consequences, postacute sequelae of SARS-CoV-2 infection appears to be a pandemic of its own, impacting up to one-third of survivors and often causing symptoms suggestive of cardiovascular phenomena. This review will highlight the suspected pathophysiology of postacute sequelae of SARS-CoV-2, its influence on the cardiovascular system, and potential treatment strategies.

Key Words: COVID-19 ■ infections ■ pandemics ■ SARS-CoV-2 ■ survivors

Postacute sequelae of SARS-CoV-2 infection (PASC), also referred to as long COVID, long-haul COVID, and post-COVID syndrome, is defined by the Centers for Disease Control and Prevention as a syndrome of mental and physical health symptoms presenting ≥4 weeks after acute SARS-CoV-2 infection.[1] However, definitions are variable with respect to the onset and duration of PASC symptoms. The World Health Organization defines PASC as a diagnosis of exclusion with syndrome onset at 3 months after acute SARS-CoV-2 infection and symptom duration a minimum of 2 months.[2] The National Institute for Health and Care and Excellence in the United Kingdom defines PASC, also considered a diagnosis of exclusion, as a syndrome occurring for >12 weeks after SARS-CoV-2 infection.[3] The American College of Cardiology defines PASC as a disorder with symptoms persisting for 4 to 12 weeks (postacute period) and >12 weeks (chronic period) after SARS-CoV-2 infection. The American College of Cardiology has created subclassifications of PASC to distinguish between cardiovascular disease (CVD) and cardiovascular symptoms (CVS) unexplained by initial testing occurring during this time frame.[4] As a result, the actual prevalence of PASC varies widely, partly from variability in definition and underdiagnosis. For the sake of this review, the PASC definition and taxonomy proposed by the American College of Cardiology will be utilized.

A Centers for Disease Control and Prevention review of electronic health record data found that 1 in 5 adults between ages 18 and 64 years and 1 in 4 adults ≥65 years had a diagnostic code associated with post-COVID symptoms 30 days after onset of SARS-CoV-2, though this study likely underestimates the prevalence of PASC, as it did not include billing codes for individual symptoms commonly associated with PASC.[5] One study that did account for these symptoms reported a prevalence between 10% and 15%.[6] A cross-sectional study conducted between February 2021 and July 2022 evaluating 16091 survey respondents aged ≥18 residing in the United States suggested that PASC was most prevalent and associated with female sex and older age with diminished risk after completing the SARS-CoV-2 vaccination series before infection.[7]

Remarkably, the severity of acute SARS-CoV-2 infection does not directly correlate with the severity of PASC, thus adding to the complexity of this postinfectious phenomenon. Symptoms are often both expansive and multisystemic and include, but are not limited to, total body fatigue, exercise intolerance, dyspnea, palpitations, chest discomfort, sleep disturbance, cognitive dysfunction or brain fog, gut dysmotility (constipation and diarrhea), neuropathy, myalgias, arthralgias, migraines, dermatologic manifestations, and endocrine-related symptoms (eg, cold/heat intolerance, alterations in menstruation[8];

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Nonstandard Abbreviations and Acronyms

ACE2	angiotensin-converting enzyme 2
AutoAb	autoantibody
CFS	chronic fatigue syndrome
cMRI	cardiac magnetic resonance imaging
CPET	cardiopulmonary exercise testing
CT	computed tomography
CVD	cardiovascular disease
CVS	cardiovascular symptom
IL	interleukin
ME	myalgic encephalomyelitis
PASC	postacute sequelae of SARS-CoV-2
POTS	postural orthostatic tachycardia syndrome
TNFα	tumor necrosis factor alpha

Figure 1). Mental health consequences include anxiety, depression, suicidal ideation, posttraumatic stress disorder, and neurocognitive decline.[9]

ACUTE CARDIOVASCULAR EFFECTS OF SARS-COV-2 INFECTION

Acute Clinical Cardiovascular Sequelae

Clinical presentations of acute SARS-CoV-2 infection include common CVS such as chest pain, dyspnea, palpitations, exertional intolerance, and fatigue. The acute cardiovascular impact of SARS-CoV-2 includes myocardial ischemia, stress cardiomyopathy, left or right ventricular dysfunction including cardiogenic shock, myocarditis and pericarditis, cardiac arrhythmias, venous and arterial thromboembolic phenomena due to viral-mediated coagulopathy, and multisystem inflammatory syndrome in both children and adults[10–13] (Figure 2). Echocardiographic studies have revealed both left and right ventricular dysfunction, diastolic dysfunction, and pericardial effusion.[14] Studies suggest individuals with significant cardiovascular comorbidities are more likely to require hospitalization and are more susceptible to increased risk of complication and death.[15,16] Troponin elevations, occurring in ≈20% to 30% of patients hospitalized with COVID-19, appear to correlate with 2 to 5× increased risk of death and have been shown to be a consequence of predominantly type 2 MI rather than acute coronary syndromes.[13,17,18]

In addition, myocarditis from acute SARS-CoV-2 infection, previously thought to be highly prevalent, has now been shown to be exceedingly rare, seen in <4.5% of autopsy cases in nonathletes and even lower via cardiac magnetic resonance imaging (cMRI) in competitive athletes with an estimated prevalence of 0.6% to 0.7%.[19–21] Investigators of the Big Ten COVID-19 Cardiac Registry assessed 1597 collegiate athletes at 13 universities and found only 2.3% (37 athletes) were diagnosed with both clinical and subclinical myocarditis by cMRI; of these athletes, only 5 had cardiac symptoms, correlating to a detected prevalence of 0.31%.[22] Additional registries by Moulson et al[20] and Daniels et al[22] have shown myocarditis incidences of 0.4% (12/2820) and 2% (37/1597), respectively, among collegiate athletes. Finally, of 3393 collegiate athletes from the Outcomes Registry for Cardiac Conditions in Athletes, only 0.1% (5), who endorsed chest pain, had evidence of cardiac involvement by cMRI; no athlete reporting exertional symptoms without chest pain had probable or definitive cardiac involvement by cMRI.[23]

The Outcomes Registry for Cardiac Conditions in Athletes also discovered that 4.0% (137) of collegiate athletes reported exertional symptoms upon return to exercise, with shortness of breath (58%), chest pain (36%), and exercise intolerance (23%) being the most common, followed by palpitations (7%) and presyncope/syncope (4%). Persistent symptoms, defined as >3 weeks after the SARS-CoV-2 infection, were reported in only 1.2% (44) of athletes with shortness of breath (20%), chest pain (15%), and fatigue (10%) among the most common. Athletes with exertional symptoms completed advanced diagnostic testing inclusive of both cardiac and pulmonary imaging (cMRI, stress test, coronary computed tomography [CT] angiogram, cardiopulmonary exercise testing [CPET], ambulatory rhythm monitoring, pulmonary function tests, chest radiograph, CT pulmonary embolism) with 93.4% having normal testing. Positive results led to diagnoses of pneumonia (2), inappropriate sinus tachycardia (2), and pleural effusion (1).[23]

Acute Vascular Dysfunction and Thrombotic Complications

Thromboembolic events in hospitalized patients with acute SARS-CoV-2 infection are common with 1 study of >3000 patients hospitalized consecutively showing stroke, deep vein thrombosis, and pulmonary embolism in 1.6%, 3.9%, and 3.2%, respectively.[24] Venous and arterial thrombosis appear to be a consequence of increased expression of ACE2 (angiotensin-converting enzyme 2) receptors on arterial and venous endothelium triggering localized viral replication, macrophage activation, and the release of proinflammatory cytokines such as IL (interleukin)-1β, IL-6, and TNFα (tumor necrosis factor alpha).[25] Subsequent endothelial dysfunction and inflammation (ie, endotheliitis) are associated with increased levels of von Willebrand factor, tissue factor, and plasminogen activator inhibitor-1, thus propagating a prothrombotic state and vascular injury/vasculitis. Conversely, while the first report of platelet hyperreactivity by SARS-CoV-2 gained much attention,[26] it was later revealed by collaborative groups that while the ACE2 receptor is clearly located on the surface of human

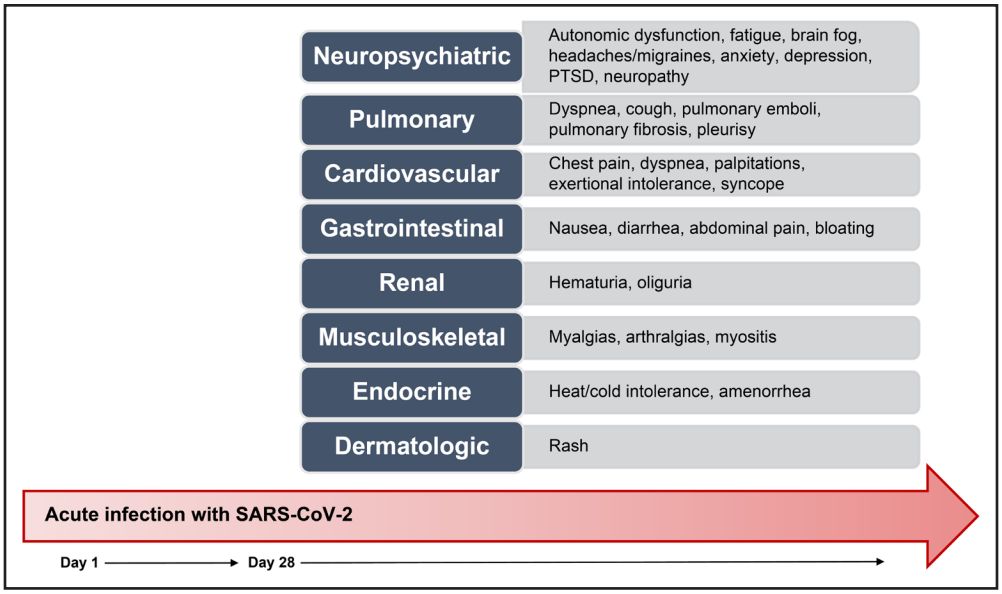

Figure 1. Multisystemic involvement in postacute sequelae of SARS-CoV-2 infection (PASC).
The Centers for Disease Control and Prevention define PASC as a syndrome of persistent, multisystemic SARS-CoV-2 symptoms beyond 28 days from initial infection. PTSD indicates posttraumatic stress disorder.

platelets, ACE2 is not required for viral entry, and viral entry ultimately caused platelet apoptosis, triggering dysregulated immunity to mediate thrombosis rather than through platelet aggregation as was initially suggested.[27] This mechanistic observation was later substantiated by high-quality clinical trials that revealed antiplatelet medications failed to significantly affect mortality or thrombotic morbidity in COVID-19.[28,29] Thus, platelets were abandoned as meaningful therapeutic targets of thrombosis by SARS-CoV-2. Elevated D-dimer levels in peripheral blood is a significant indicator of the breakdown of fibrin, thus confirming coagulopathy brought on by acute SARS-CoV-2 infection.[25,30,31] Autopsy data showing microthrombi in all organ systems (eg, cardiovascular, pulmonary arteries, prostate, hepatic portal and sinusoidal vessels, glomerular capillaries, alveolar arterioles) further reiterate virus-induced coagulopathy and microvascular dysfunction[32–35] (Figure 3).

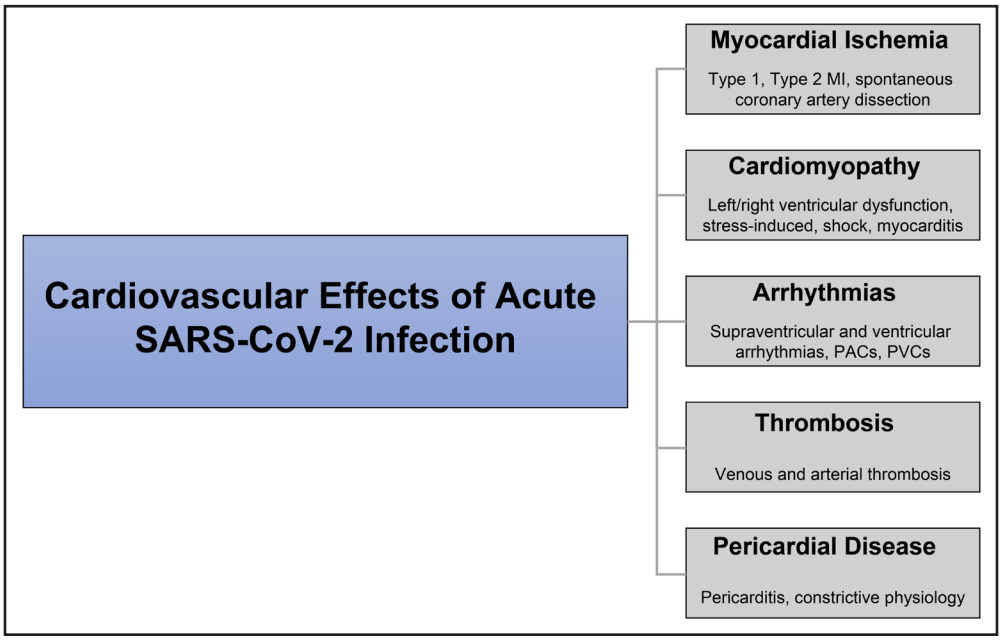

Figure 2. Cardiovascular effects of acute SARS-CoV-2 infection.
Acute SARS-CoV-2 has been associated with type 1 and 2 myocardial infarct (MI) and ischemia, cardiomyopathy, myocarditis, cardiogenic shock, atrial and ventricular arrhythmias, venous and arterial thromboembolic events, and pericardial disease. PAC indicates premature atrial contraction; and PVC, premature ventricular contraction.

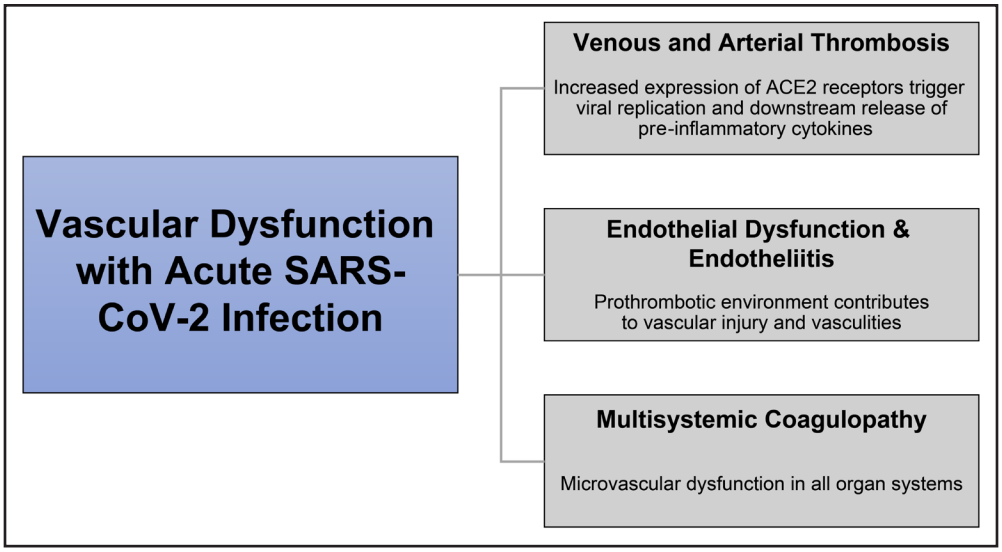

Figure 3. Vascular dysfunction with acute SARS-CoV-2 infection.
Thrombosis arises from increased expression of venous and arterial endothelial ACE2 (angiotensin-converting enzyme 2) receptors leading to local viral replication, macrophage activation, and proinflammatory cytokine release. A prothrombotic environment leads endothelial dysfunction/vascular injury in multiple organ systems (eg, cardiovascular, pulmonary, hepatic, and nephrotic).

CHRONIC CARDIOVASCULAR EFFECTS OF SARS-COV-2 INFECTION

Chronic Clinical Cardiovascular Sequelae

PASC-CVS is inclusive of CVS in the absence of cardiovascular pathology on diagnostic testing. Symptoms include but are not limited to chest pain, palpitations, dyspnea, exercise intolerance, tachycardia, lightheadedness, and syncope (Figure 4). In one study that evaluated symptoms 60 days after acute SARS-CoV-2 infection, 21.7% of patients reported ongoing chest pain and 43.4% reported persistent dyspnea.[36] Another study of 150 patients with noncritical polymerase chain reaction–confirmed COVID-19 infection between March and June 2020 showed that 18% and 13.1% of individuals reported chest pain 30 and 60 days, respectively, after acute infection; palpitations were reported in 6.5% and 10.9% at 30 and 60 days, respectively.[37] In a study evaluating 1733 hospitalized patients in Wuhan, China, 5% to 9% had chest pain and palpitations, and 26% reported breathlessness persisting at 6 months post-infection. After 1 year, 30% and 7% of individuals continued to report breathlessness and chest pain, respectively.[38] A UK study in late 2020 evaluated 1077 hospitalized patients and found that 5 months after hospital discharge, 21% to 28% had persistent chest pain and palpitations and 41% had ongoing dyspnea.[39]

Although the incidence of PASC-CVS among sedentary individuals appears quite significant, retrospective studies suggest that PASC-CV symptoms may be rarer in athletes, although the number of athletes with post-COVID symptoms may be underreported. A recent systematic review and meta-analysis of acute/postacute COVID-19 presentations in athletes included 11518 athletes from 43 studies published from 2019 to January 6, 2022, of which only 5% completed cardiac testing.[40] Results from the Outcomes Registry for Cardiac Conditions in Athletes show that only 2 athletes (0.06%) reported symptoms persisting beyond 12 weeks.[23] While PASC-CVS among athletes is significantly lower than that of sedentary individuals, it has yet to be shown that increased exercise capacity and athleticism may be protective against developing post-COVID syndrome or severe PASC symptoms.

It is important to acknowledge that numerous studies of post-COVID syndromes and symptoms may be limited in design.[41] Many are based on differing definitions of PASC, variability in time of analysis, small sample size, and lack of control groups and may reflect significant recall bias leading to marked heterogeneity in reported results. Additionally, new PASC symptoms continue to surface and demonstrate a wide spectrum of symptom severity, thus posing difficulty in capturing true reflections of the syndrome and the affected population. Consequently, more data are required to accurately show the epidemiology of PASC, patient characteristics that correlate to greater risk for PASC, PASC symptoms in their entirety, and their relation to CVDs.

Chronic cardiovascular effects of SARS-CoV-2 infection due to a cardiac cause (PASC-CVD) may include myocardial injury, myopericarditis, heart failure, arrhythmias, and vascular complications (ie, arterial and venous thromboembolism, vasculitis). There is growing evidence that individuals with cardiovascular comorbidities may be at increased risk of death due to SARS-CoV-2.[42] Autopsy data in such individuals have shown evidence of myocardial hypertrophy (92.9%) with 7.1% of patients having transthyretin cardiac amyloidosis, 21.4% focal myocardial

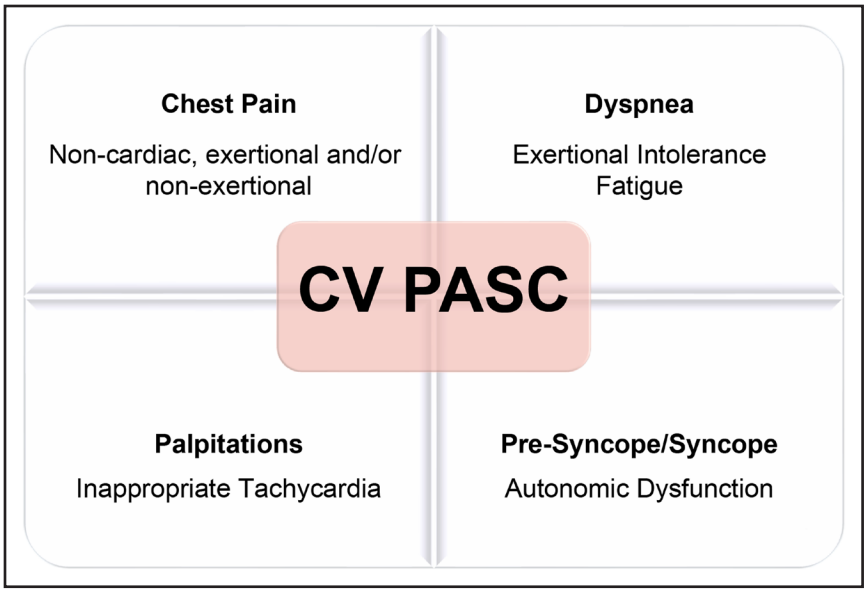

Figure 4. Cardiovascular postacute sequelae of SARS-CoV-2 (PASC). Cardiovascular (CV) PASC consists of cardiovascular symptoms in the absence of cardiovascular pathology. Symptoms include chest pain, palpitations, (exertional) dyspnea, presyncope/syncope.

fibrosis, and 100% mild-to-severe coronary artery disease with 21% having had acute myocardial infarction.[43]

To date, the incidence of postacute myocarditis and pericarditis has been shown to be much lower than previously thought. In a retrospective study of 196 662 adults with COVID-19 infection between March 2020 and January 2021, only 9 post-COVID patients (0.0046%) and 11 post-COVID patients (0.0056%) developed myocarditis and pericarditis, respectively, compared with 27 patient-controls who had myocarditis (0.0046%) and 52 patient-controls with pericarditis (0.0088%), thus suggesting there is no association between post–COVID-19 infection and both myocarditis and pericarditis.[44] Another study of 153 760 US Veterans from the US Department of Veterans Affairs national health care databases showed that the incidence and estimated 12-month burden of myocarditis and pericarditis were the lowest among patients with cardiovascular outcomes, including dysrhythmias, ischemic heart disease, cardiomyopathy and cardiogenic shock, and thrombotic disorders, at least 30 days beyond a positive COVID-19 test.[45]

Long-Term Atherothrombotic Risk After COVID-19

Dyspnea, chest pain, and excessive fatigue are among the most frequently reported symptoms of PASC, affecting ≈25% of survivors.[46] The extent to which these symptoms are derived from cardiac, pulmonary, or systemic processes and whether they represent protracted immune, vascular, neuroendocrine, or emergent mechanisms remains uncertain. However, it has become increasingly clear that survivors of COVID-19 have elevated risk of discrete cardiovascular events, including acute myocardial infarction and stroke, and this risk appears to extend months into recovery from the acute illness.

It is long established that the population-level rates of acute coronary syndrome increase with seasonal respiratory viral infections and are driven, in part, by innate immune activation leading to typical presentations of atherothrombosis.[47,48] From a cardiovascular standpoint, COVID-19 has similarities to influenza but with several important distinctions. For instance, Xie et al[49] have shown that the rates of most adverse events, including cardiac injury (odds ratio, 1.75 [1.50–2.05]) and stroke (1.62 [1.17–2.24]), were higher during the first wave of COVID-19, compared with historical influenza infections. An estimated 20% of those hospitalized with COVID-19 have cardiac injury as demonstrated by cardiac-specific troponin elevations.[50] However, a broad range of cardiac effects are caused by COVID-19. At autopsy in those who succumb to COVID-19, at least 1 myocardial abnormality was present in 47.8% of cases but with substantial heterogeneity in histopathologies.[51] For instance, the rate of myocarditis was reported to be 7.2%, nonmyocarditis inflammation was observed in 12.6%, single-cell ischemia, referring to scattered individual myocyte necrosis, was seen in 13.7%, small vessel thrombi in 10.8%, and macrothrombi in 19.1%.[51] Even within a narrower clinical setting such as those undergoing invasive coronary angiography for ST-segment–elevation myocardial infarction, a clear epicardial culprit lesion was absent in 35%.[52,53] These data support the contention that cardiac injury during COVID-19 is only infrequently caused by classic atherothrombotic plaque rupture.[54] Thus, the cardiovascular risk and operative mechanisms in the setting of COVID-19 appear to be more complex and differ quantitatively and qualitatively from typical seasonal respiratory infections.

Studies also suggest that the duration of elevated cardiovascular risk may be longer after COVID-19 than after other respiratory viruses. Whereas the risk of acute myocardial infarction with influenza appears limited to 7 days

after laboratory confirmation,[55] several studies now suggest COVID-19 is associated with a protracted period of CVD risk. For instance, in a large cohort study in Sweden, Katsoularis et al[56] showed the incident rate ratio of acute MI to be 2.89, 2.5, and 1.6 in weeks 1, 2, and 3 to 4, respectively. Within the US Veterans Health Administration (n=153 760), Xie et al[45] show that elevated rates of acute myocardial infarction (hazard ratio, 1.63 [95% CI, 1.51–1.75]) and stroke (hazard ratio, 1.52 [95% CI, 1.43–1.62]) extend beyond 30 days from SARS-CoV-2 infection.

It remains unclear from these epidemiologic studies whether post–COVID-19 atherothrombotic events stem from protracted immunothrombotic activation on the heels of the index infection (ie, failed convalescence, viral persistence), lifestyle changes or medication nonadherence post-infection, versus truly emergent immunothrombotic mechanisms (ie, reactivation of latent infections and autoantibodies) potentially specific to SARS-CoV-2.

PATHOGENIC THEORIES IN PASC

AutoAb Hypothesis

The pathophysiologic mechanisms behind acute cardiovascular involvement with SARS-CoV-2 appear to be largely predicated upon the release of proinflammatory cytokines and subsequent cytokine storm provoking increased vascular permeability, endothelial dysfunction, and dysregulated coagulation along with increased risk of thrombosis.[57,58] Another hypothesis suggests macrophage-predominant infiltration with low lymphocytic involvement in the acute inflammatory process.[59] Histopathology from 24 confirmed SARS-CoV-2 cardiac autopsy samples compared with 16 age-matched influenza H1N1 A cardiac samples, 8 lymphocytic noninfluenza myocarditis, and 9 noninflamed heart tissues revealed that viral myocarditis was not evident in the SARs-CoV-2 samples; rather, there was a significant increase in perivascular CD11b/TIE2+ macrophages, a finding not seen in the 3 comparison groups, suggesting that cardiac involvement in SARS-CoV-2 may be predicated upon a macrophage-driven inflammatory process.[60] Additional studies suggest that the inflammatory response in acute SARS-CoV-2 infection provokes AutoAb (autoantibody) production targeting cardiac antigens. In one study of 104 patients hospitalized with COVID-19, 68% (71) had anticardiac autoAbs: 39% had anticardiac IgG autoAbs, 51% had anticardiac IgM autoAbs, and 22% had both. Of the 40 patients with dilated cardiomyopathy and 20 patients with severe aortic stenosis who comprised the control group, those with heart failure had similar levels of IgG autoAbs (45%) and significantly less IgM autoAbs (30%) while those with severe aortic stenosis had significantly lower levels of both IgG and IgM autoAbs (11% and 10%, respectively).[61] Thus, the results suggest that the majority of subjects hospitalized for COVID-19 developed novel anticardiac IgM autoAbs. These autoAbs may contribute to prolonged COVID-19 complications or PASC.

Antinuclear antibodies and antiphospholipid antibodies in COVID-19 and other viral infections have long been known to disturb immunologic tolerance.[62–65] AutoAbs generated during or after acute COVID infection may be drivers of immunopathogenesis with reactivity to antigens against cytokines correlating with immune response to SARS-CoV-2.[63,64,66,67] This includes antibodies that functionally inhibit interferon-stimulated gene expression via an Fc-mediated mechanism.[68] Postural orthostatic tachycardia syndrome (POTS), myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS), and complex regional pain syndrome have been associated with the detection of autoAbs and may have correlates to the tachycardia, fatigue, and chest pain syndrome symptoms experienced by patients with CV PASC. Connecting these symptoms may suggest a predilection for loss of tolerance from autoAbs to autonomic, central, peripheral nerves, cardiac muscle, vascular endothelium, or pericytes.

The role of antiphospholipid antibodies in immune-mediated thrombosis is well established.[69–72] These antibodies react with and have been reported to activate endothelial cells, monocytes, neutrophils, and platelets and are generally considered the most common cause of acquired thrombophilia. Antiphospholipid antibodies have been described in many series of patients with COVID-19[73]; their presence may be associated with disease severity,[74] though their clinical impact on the incidence of thrombosis or the outcome of a COVID-19 infection remains uncertain.[75,76] However, IgG isolated from patients with COVID-19 has been shown to activate neutrophils, induce release of neutrophil extracellular traps, and stimulate thrombosis in mice.[64,77] In contrast, there is, to this point, little information available concerning antiphospholipid antibodies in the post-COVID syndrome.[78]

Autonomic dysfunction is suspected to contribute to postural tachycardias and ME/CFS in PASC. Prior viral infection has been one of the potential triggers implicated in POTS,[79] with reports of autoAbs against ganglionic acetylcholine, G-protein coupled, muscarinic cholinergic, and angiotensin II type 1 receptors in POTS.[80–83] Among 55 patients with POTS, 91% had such autoAbs,[82] and autoAbs were associated with significant elevations of inflammatory markers of the innate immune system, suggesting ongoing inflammation.[84] Another study showed those with PASC with symptoms of CFS, POTS, and autonomic dysfunction had evidence of antibodies against the β2-adrenoceptor, muscarinic M2 receptor, angiotensin II AT1 receptor, and ACE2/angiotensin (1–7)/Mas receptor.[85] Furthermore, immune dysregulation in POTS and ME/CFS has frequently been described as including changes in cytokine profiles and immunoglobulin levels, T- and B-cell phenotypes, and a decrease of natural killer cell cytotoxicity.[86] As autoAb presence may be ubiquitous

and abundant, studies to determine their specificity and pathogenicity in PASC are imperative.[87]

Autonomic Nervous System

Autonomic dysfunction has emerged as a debilitating long-term phenomenon from COVID-19 and is characterized by symptoms that include those seen in CV PASC: lightheadedness/dizziness, syncope, dyspnea, tachycardia, exercise intolerance, atypical chest pain, and headaches.[88,89] Importantly, acute COVID-19 disease severity does not appear to directly correlate to severity in autonomic dysfunction. Several unconfirmed pathophysiologic mechanisms for autonomic dysfunction and POTS seen with PASC include hypovolemia-induced increase in cardiac sympathetic noradrenergic system outflow, neuropathy from destruction of extracardiac postganglionic sympathetic noradrenergic system neurons, autoimmune response to the virus, and invasion of the brain stem with subsequent increase in central sympathetic outflow.[90] Autonomic disorders may also be related to autoAbs (AutoAb Hypothesis) and additional, underlying autoimmune disorders.[91]

Due to limited understanding of the mechanism by which COVID-19 induces autonomic dysfunction, notably with marked heterogeneity in disease severity, many individuals who develop these symptoms after the acute infectious phase may be considered deconditioned in the absence of any diagnostic cardiac testing, subsequently remaining unidentified and untreated. Individuals may also be misdiagnosed due to significant overlap with other disorders characterized by autonomic dysfunction, which include POTS, orthostatic dysfunction, and ME/CFS.[92] Several studies also suggest that autonomic disorders may materialize after viral triggers, such as SARS-CoV-2.[93,94] Use of the Composite Autonomic Symptom Score-31 questionnaire in individuals with PASC has shown significant utility in identifying autonomic symptoms and providing a basis for therapeutic management and longitudinal assessment.[95] In a survey of 2413 adults between 18 and 64 years of age with PASC after confirmed positive testing for SARS-CoV-2, 66% had a Composite Autonomic Symptom Score-31 >20 suggesting moderate-severe autonomic dysfunction independent of the severity of acute infection and requirement of hospitalization.[96]

Physical Deconditioning

In the absence of cardiopulmonary abnormalities and PASC-CVD, unexplained exertional cardiopulmonary symptoms may be consequences of relative cardiac deconditioning. Gaffney et al[97] initially described cardiovascular deconditioning as evidenced by increases in heart rate, central venous pressure, cardiac output, and stroke volume after merely 20 hours of bed rest, albeit this study was of only 5 men within the age range of 41 to 48 years. Subsequent studies of individuals with prolonged bed rest and space flight have demonstrated reduction in stroke volume, cardiac output, blood volume, left ventricular mass, leading to exertional signs and symptoms such as dyspnea, exertional intolerance, and tachycardia.[98–100] In addition, signs and symptoms of deconditioning and autonomic dysfunction may overlap or exacerbate one another. For instance, orthostatic intolerance often seen in individuals with autonomic dysfunction may be a direct consequence of bed rest precipitating a reduction in plasma volume, baseline pulmonary capillary wedge pressure, left ventricular end diastolic volume, and excessive decline in stroke volume while upright.[98] Given the similarity in findings between autonomic dysfunction and deconditioning, it is imperative that the latter remains in the differential, though as a diagnosis of exclusion.

Persistence of the SARS-CoV-2 Viral Signature

Ongoing inflammatory processes may also be triggered by persistence of viral fragments, which are known to be shed as long as months after the acute infection in the stool, or a less robust immune response to the acute SARS-CoV-2 infection.[101] Reports support prolonged shedding of SARS-CoV-2 viral RNA in the stool and prolonged persistence in body reservoirs.[102–105] In 1 study of 661 individuals with laboratory-confirmed COVID-19 infection and minimal-to-no symptoms, there appeared to be a correlation between an elevated aspartate transaminase level at least twice the upper limit of normal and a longer duration of viral shedding.[106] These viral fragments may provoke hyperimmune responses that manifest into symptoms of PASC and CV PASC.

Oxidative Stress and Mitochondrial Dysfunction

Symptoms of CV PASC and autonomic dysfunction may also be related to oxidative stress and alteration in cardiorespiratory function.[107] Oxidative stress leads to damage of cellular components, and nitrosative stress contributes to S-nitrosylation of several biomolecules including lipids, proteins, and DNA, which can induce cellular apoptosis, impact vasodilatory responses, and consume antioxidant species.[108,109] A decreased level of antioxidants, such as glutathione, cysteine, selenium, and vitamin C, may be seen in syndromes such as ME/CFS.[110–112]

Mitochondrial dysfunction triggered by SARS-CoV-2 contributes to the upregulation of glycolysis and decrease in oxidative phosphorylation as evidenced by elevated blood lactate post-exercise compared with controls and elevated serum lactate dehydrogenase.[113,114] These changes manifest a hypometabolic state characteristic of ME/CFS.[115] Muscle biopsies in patients with ME/CFS have shown structural mitochondrial abnormalities such

as fusion of mitochondrial cristae.[116] Additional studies suggest deletions of mitochondrial DNA and correlations between specific symptoms and certain single-nucleotide polymorphisms.[117] These findings in ME/CFS may be relevant to SARS-CoV-2 and CV PASC. Viral replication and reactivation appear to precipitate a hyperinflammatory state with a cytokine storm in the acute phase, mitochondrial dysfunction and impairments in oxidative phosphorylation, and oxidative and nitrosative stress, clinically manifesting as extreme fatigue, exertional intolerance, lightheadedness, endothelial dysfunction, and autonomic dysregulation.[118]

Immunothrombotic Drivers

Innate immune responses, thrombophilia/fibrinolysis, and endothelial function are linked via pathways with the potential for sustained, feedforward activation. For instance, the exposure of pathogen- or danger-associated molecular patterns induces the expression of a variety of proinflammatory cytokines and also directly activates monocytes and neutrophils.[119] The expansion of CD16+ inflammatory/nonclassical monocyte subsets and activated neutrophils is capable of engaging activated platelets, expressing tissue factor, inducing complement, and stimulating NETosis to disrupt endothelial barriers and cause vasoactive dysfunction.[119–124] Secondary inflammatory processes may derive from microvascular injury, cardiometabolic stimuli, oxidative stress, and neuroendocrine activation, which may complicate or delay convalescence from a primary exposure.[125] T cells, especially memory subsets with vascular homing properties, may also contribute to an immunothrombotic milieu.[126]

Although studies have described the importance of these pathways in acute COVID-19, less is known about the kinetics of detuning after infection.[127] Recent studies suggest ongoing immunothrombotic activation may persist for months after COVID-19 and may be associated with PASC. For instance, Patterson et al[128] found that those with PASC had greater CD16+ monocyte proportions in the blood and these cells harbored the S1 protein up to 15 months after infection. In another study, Kruger et al[129] found PASC to be associated with fibrin amyloid microclots. However, additional studies are needed to validate these findings in larger cohorts, determine the drivers of persistent immunothrombotic activation, and identify interventions that can safely detune these mechanisms.

Vascular/Endothelial Hypothesis

Venous and arterial thrombosis has been a prominent feature of acute SARS-CoV-2 infection.[24,130] Viral infection, inflammation, and degranulation of endothelial cells have been visualized by electron microscopy. Inflammation of vascular endothelial cells (endotheliitis) leads to degranulation and exocytosis of Weibel-Palade bodies containing von Willebrand factor, which promotes recruitment of platelets and platelet aggregates through the glycoprotein 1b receptor; IL-8 and other inflammatory endothelial cytokines are also released in this manner.[131] Several studies of the multisystemic manifestations of the disease and prothrombotic manifestations of acute COVID-19 support a role for vascular or endothelial dysfunction in PASC, particularly in the microvasculature. Platelet serotonin release likely impacts endothelium, causing endothelium and non–endothelium-dependent changes in vascular tone and inflammation with long-term changes in vasoreactivity that may contribute to PASC symptoms of dysautonomia resembling POTS.[132] Since endothelial dysfunction in POTS is readily apparent with noninvasive techniques including venous occlusion plethysmography, brachial artery reactivity testing, and digital plethysmography,[133,134] these can be used to explore prolonged, long-term vascular consequences of COVID-19 in follow-up clinical studies (Figure 5).

PROPOSED DIAGNOSTIC AND THERAPEUTIC STRATEGIES FOR CV PASC

Diagnostic Testing

Symptoms of CV PASC overlap with those suggestive of cardiopulmonary disease/pathology. Consequently, diagnostic testing should be predicated upon inclusion or exclusion of pulmonary disease, myocardial ischemia, heart failure, inflammatory syndromes such as myocarditis or pericarditis, and arrhythmias.

Initial pulmonary evaluation may include a chest radiograph followed by more advanced diagnostic imaging such as CT pulmonary angiography, high-resolution CT, pulmonary function tests, ventilation/perfusion scan, 6-minute walk test, and sleep study. Invasive testing such as right heart catheterization and CPET may be advised for assessment of pulmonary hypertension.

Initial cardiac evaluation may include a 12-lead electrocardiogram alongside cardiac imaging such as transthoracic echocardiography with downstream testing more specific for symptoms: stress testing, including invasive or noninvasive CPET, for evaluation of chest pain syndromes, exertional dyspnea, or exertional intolerance; ambulatory rhythm monitoring to assess palpitations, lightheadedness/dizziness, presyncope/syncope; advanced cardiac imaging (eg, cMRI, coronary CT angiography, positron emission tomography) for structural and functional cardiac assessment including evaluation of myocardial/pericardial edema, myocardial injury, myocardial infarction, microinfarcts, and scar.[135] Laboratory testing including high-sensitivity cardiac troponin assays, erythrocyte sedimentation rate,

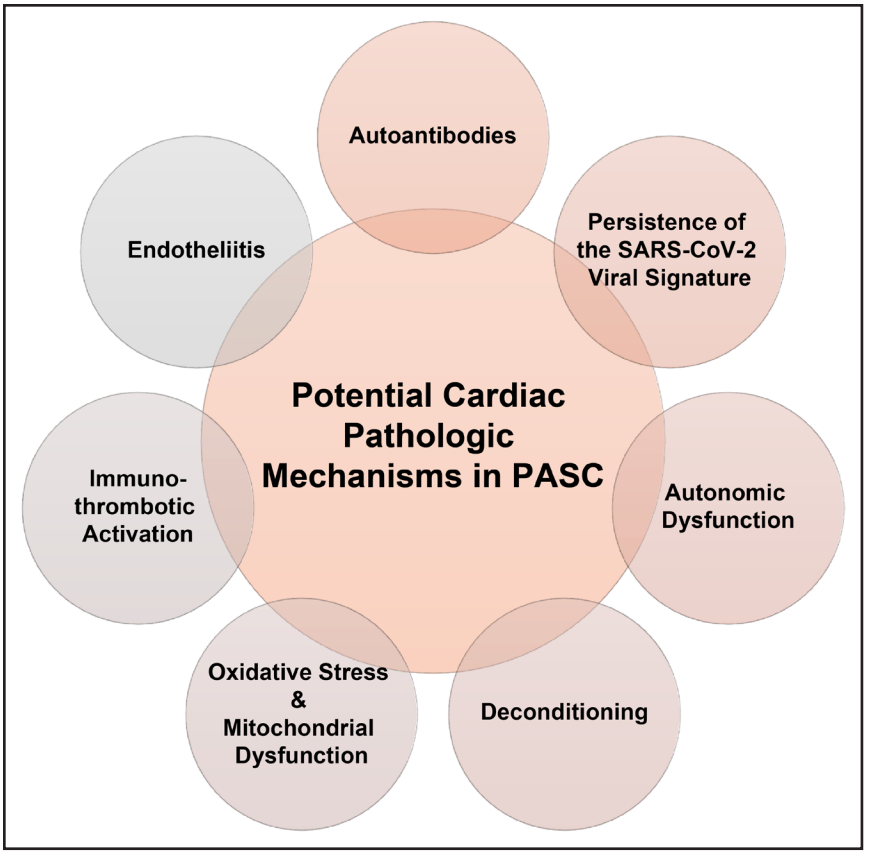

Figure 5. Potential pathophysiologic mechanisms of postacute sequelae of SARS-CoV-2 (PASC).

C-reactive protein, N-terminal pro-B-type natriuretic peptide, and D-dimer may potentially provide insight into the presence of underlying inflammation. In cases where suspicion of thromboembolism is heightened, arterial or venous duplex ultrasound, CT imaging for acute embolism, or ventilation/perfusion scanning may have diagnostic yield. Finally, invasive cardiac testing such as coronary angiography, endomyocardial biopsy, and electrophysiology studies may be performed depending upon initial cardiac diagnostic study results and suspicion of coronary disease, myocardial disease, and arrhythmogenic disease.[136,137]

In most cases of PASC-CVS, cardiac testing for primary cardiac pathology may be unrevealing. Consequently, additional investigation of symptoms may be based upon the most prominent symptoms. In individuals presenting with multisystemic symptoms suspicious for autonomic dysfunction, more specialized testing with an autonomic specialist should be pursued and may include a 10-minute stand test, orthostatics, tilt table testing, deep breathing test, Valsalva maneuver, skin biopsy and thermoregulatory sweat test to assess for small fiber neuropathy, and quantitative sudomotor axon reflex testing[138] (Figure 6).

CPET is proving to become a useful diagnostic tool for evaluation of symptoms of exertional intolerance, fatigue, or dyspnea due to its ability to assess the multisystemic response to exercise—cardiac, pulmonary, and neuromuscular. Case reports and case series suggest that individuals with PASC-CVS or PASC-CVD have reduced oxygen consumption at maximal effort with early anaerobic threshold, reduced oxygen consumption/work rate, and blunted oxygen pulse (oxygen consumption/heart rate), suggesting relative cardiac deconditioning.[139,140] However, a diagnosis of deconditioning may be incomplete, particularly in individuals with virally mediated mitochondrial dysfunction and autonomic dysfunction. Invasive CPET with arterial blood sampling to measure cardiac output, peripheral oxygen extraction, and blood lactate can provide more specific details regarding the cause for exertional intolerance. For instance, exertional intolerance due to limited oxygen extraction by peripheral musculature is likely a consequence of mitochondrial dysfunction.[141] Evaluation of chronotropic competence and heart rate and blood pressure variability with exercise can delineate autonomic dysfunction from alternate mechanisms of disease. In a study of 205 individuals referred to a post–COVID-19 center, 25% had findings consistent with autonomic dysfunction on CPET: significantly reduced work rate and peak oxygen consumption and ventilatory inefficiency.[142] As a result, CPET appears to be a promising tool for delineating the pathogenesis for exertional intolerance and poor cardiorespiratory fitness in patients presenting with symptoms suggesting of PASC-CVD.

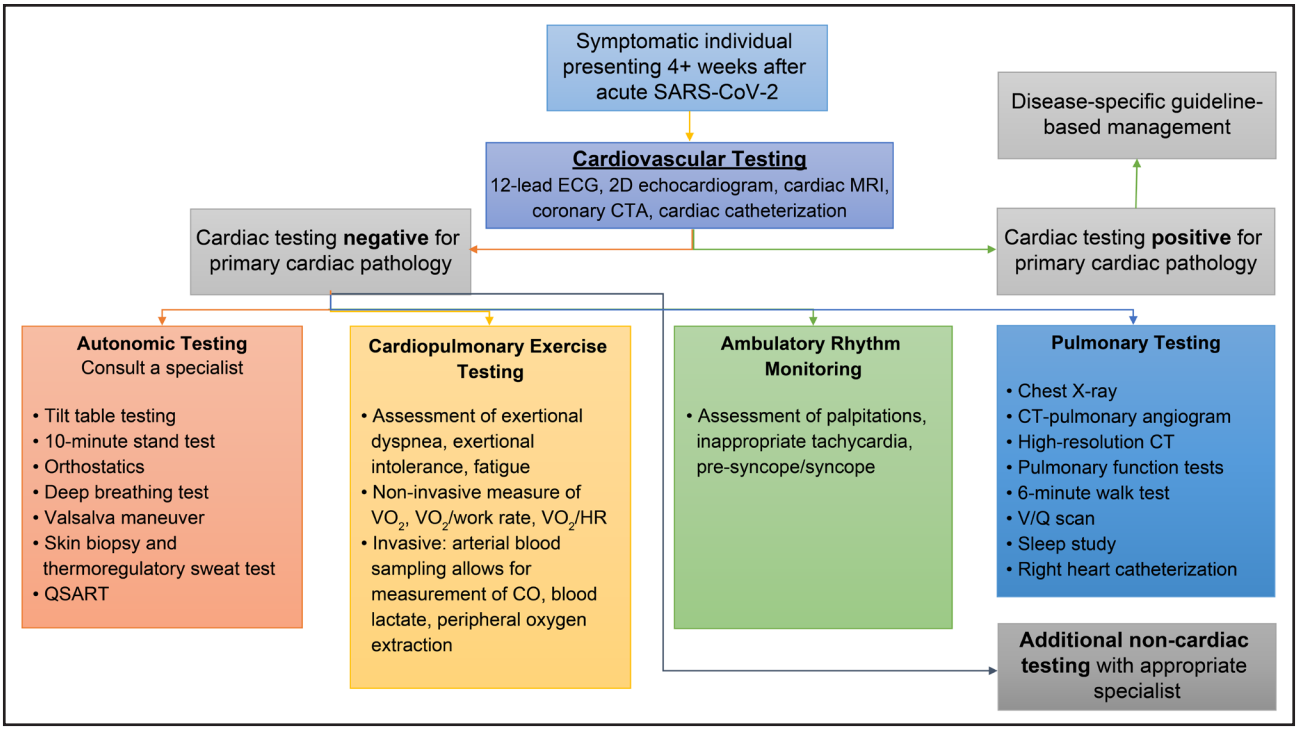

Figure 6. Diagnostic evaluation of cardiovascular symptoms at least 4 weeks after acute SARS-CoV-2 infection.
2D indicates 2 dimensional; CO, cardiac output; CT, computed tomography; CTA, computed tomography angiography; HR, heart rate; MRI, magnetic resonance imaging; QSART, quantitative sudomotor axon reflex testing; V/Q, ventilation/perfusion; and VO_2, oxygen consumption.

cMRI is the gold standard noninvasive imaging tool for structural and functional cardiac evaluation. Amidst the pandemic, it has been used to understand the cause for elevated troponin levels in individuals with COVID-19 infection. In a prospective case-control study of 342 patients with COVID-19 and elevated troponin within 28 days of discharge from 25 hospitals in the United Kingdom between June 2020 and March 2021 compared with (1) 64 patients with COVID-19 and normal troponin levels and (2) 113 patients without COVID-19 and normal troponin levels, the frequency of any cardiac abnormality was twice as high in patients with COVID and elevated troponin levels.[135] Of the cases, 17.2% had ventricular dysfunction (3.1% and 7.1% among controls) with mild (left ventricular ejection fraction, >50%), moderate (left ventricular ejection fraction, 40%–50%), and severe (left ventricular ejection fraction, <40%) left ventricular dysfunction seen in 3.0%, 8.9%, and 5.3% of cases, respectively. Right ventricular dysfunction was found in 26.2% of cases. Furthermore, 6.7% of cases had probable recent myocarditis per Lake Louise MRI Criteria (versus 1.7% controls without COVID-19; P=0.045), and 42% of cases had scar versus 7% and 23% among controls (P<0.001). Notably, cases appeared to have a distinct pattern of myocardial injury, with more cases than controls showing myocardial infarction (13% versus 2% and 7%, respectively; P<0.01) and a new pattern of microinfarction (9% in cases versus 0% and 1% in control groups; P<0.001), suggesting a prothrombotic quality of COVID-19. Cases with myocardial infarct and microinfarct patterns also had higher cardiac troponin levels than those with either no late gadolinium enhancement or those with late gadolinium enhancement patterns suggestive of myocarditis, dual pathology (infarct and nonischemic), or nonspecific pathology. Finally, myocardial scar was found to be an independent predictor of major adverse cardiovascular events.[135]

cMRI may also be used to assess mitochondrial function when paired with spectroscopy. In a prospective study of 20 patients diagnosed with PASC without underlying CVD, there was no significant difference in myocardial energetics (phosphocreatine to adenosine triphosphate ratio) when compared with matched healthy controls with no prior diagnosis of SARS-CoV-2.[143] Although this small exploratory study did not show a revolutionary difference in myocardial energetics between cases and controls, larger multicenter studies may support the capability of cMRI with spectroscopy to provide insight into energy metabolism and aid in establishing a diagnosis of mitochondrial dysfunction in individuals with CV PASC.

Therapeutic Management

Management of cardiovascular complications of SARS-CoV-2 (PASC-CVD) is comparable to strategies used outside of viral association. Invasive strategies such as coronary angiography or surgical revascularization, electrophysiologic studies and therapies, circulatory support,

and thrombectomy/thrombolysis are reserved for individuals with myocardial ischemia, symptomatic or malignant arrhythmias, heart failure requiring advanced therapies, and arterial or venous thromboembolic disease. Additionally, large multicenter studies have shown that guideline-directed medical therapy, including ACE inhibitors and angiotensin receptor blockers, does not appear to confer increased risk of persistent COVID infection or reinfection. Therapeutic anticoagulation for diagnosed thromboembolic disease is advised while prophylactic anticoagulation in an outpatient setting may pose greater risk than benefit and should be dependent upon individual risk and comorbidities.[136,137]

Due to the lack of randomized control trials studying both nonpharmacologic supportive strategies and pharmacologic intervention strategies, therapeutic management of autonomic dysfunction in individuals with PASC-CVS may resemble treatments used outside of viral association, which will be discussed here and warrant additional clinical study. Aggressive salt supplementation of 7 to 10 g daily alongside increased water consumption to at least 3 L daily to increase plasma volume and reduce sympathetic hyperactivity may be helpful. Compressive stockings and garments including abdominal binders may mitigate symptoms of orthostasis by minimizing venous pooling and central hypovolemia.[144] Counterpressure maneuvers during prolonged sitting and head of bed elevation may help manage orthostatic symptoms.[145] Diet modifications such as plant-based, gluten- and dairy-free, low-fermentable oligosaccharides, disaccharides, monosaccharides, and polyols may be tried, though supportive evidence remains limited.[146] Pharmacotherapy is dependent upon the most predominant symptom. Individuals with resting or postural tachycardia independent of orthostasis may benefit from β-blocker therapy or ivabradine, a hyperpolarization-activated cyclic nucleotide-gated channel blocker. Those with significant orthostatic intolerance may warrant blood pressure support with either midodrine—a peripheral α-1 adrenergic agonist—and both vasoconstrictor and venoconstrictor or the aldosterone analogue fludrocortisone. Pyridostigmine—a peripheral acetylcholinesterase inhibitor—has been shown to temper heart rate in response to standing in patients with POTS and improve symptoms in ≈50% of patients with POTS.[147]

Graded Exercise Program and Return to Sports Participation

Individuals, both athletes and nonathletes, with a diagnosis of clinical myocarditis are advised to refrain from exercise for a minimum of 3 to 6 months to reduce risk of sudden cardiac arrest and death. Return to exercise and competitive sports thereafter is dependent upon the presence/absence of cardiac symptoms, resolution of myocardial injury and arrhythmias at rest and with exertion, and normalization of left ventricular systolic function. Provided that cardiac testing after abstinence from exercise shows cardiac resolution, individuals may return to activity via a graded exercise protocol, with reevaluation and consideration of ME/CFS should postexertional fatigue worsen after exercise.[4]

Exercise is vital to restoring autonomic balance and improving overall functional limitation in individuals with PASC-CVS and PASC-CVD. A graded protocol incorporating aerobic and resistance training with a focus on nonupright exercises (eg, recumbent bike, rowing) can facilitate cardiac reconditioning. In a study evaluating the effects of a 6-week structured, graded exercise protocol in 31 patients with PASC, there was a significant reduction in the number of postexertional symptom exacerbation episodes from 3.4 episodes per week to 1.1 per week and a significant improvement in physical activity.[148]

Recreational and competitive athletes are not immune to PASC and consequently may develop significant physical impairment alongside physical deconditioning with persistent PASC-CVS. In fact, the prevalence of PASC symptoms is comparable to the nonathlete population with 10% of elite athletes experiencing symptoms, 27% delayed in returning to full sport participation at 4 weeks, and 6% remaining restricted after 90 days.[149] Provided that initial cardiac testing (eg, electrocardiogram, troponin, echocardiogram, ±cMRI, and CPET) shows no cardiovascular abnormality, athletes are advised to proceed with a graded protocol to return to exercise titrated by symptoms, in conjunction with psychological assessment and support. Pharmacological management of CV PASC symptoms, while not yet validated by randomized control trials to date, may be similar to nonathletes, thus inclusive of β-blocker therapy, ivabradine, midodrine, and fludrocortisone.[4]

Psychosocial Support

The psychological repercussions of the COVID-19 pandemic are expansive and transcend both acute viral infection and postacute sequelae. Consequently, the need for mental health support and treatment has exponentially grown. Anxiety, depression, posttraumatic stress disorder, and neurocognitive decline have been seen in individuals in PASC and may hinder individuals from returning to their prior level of cognitive and physical function.[150] Importantly, alternative diagnoses should be excluded before attributing PASC symptoms to psychological pathogeneses in isolation. Psychological interventions have included cognitive behavioral therapy, guided breathing exercises, mindfulness exercises, physical activity, wellness programs focused on diet, sleep hygiene, social activation, motivational interviewing, and individual coaching. Pharmacotherapy may be of additional benefit and should be utilized under the guidance of a specialist.[9]

Cardiovascular Implications of Vaccination

At present, the Centers for Disease Control and Prevention advises vaccination against SARS-CoV-2 for all individuals at least ≥5 years of age. Vaccinations have shown to be highly effective and safe with respect to acute SARS-CoV-2 infection and cardiovascular complications related to viral infection.[137] There have been few case reports and case series of myocarditis post-vaccination, typically occurring 2 to 3 days after the second mRNA vaccine dose, associated with chest pain, ST-segment abnormalities, troponin elevation, and cMRI findings consistent with myocarditis (eg, late gadolinium enhancement, myocardial edema). These cases are incredibly rare with the highest rates in men between ages 12 to 17 years (62.8 cases per million) and 18 to 24 years (50.5 cases per million). Rates in women were lower at 4.2 and 1.0 cases per million in 12- to 29-year and ≥30-year age groups, respectively. There were no reported deaths in individuals who developed postvaccination myocarditis.[151]

There is some suggestion that PASC symptoms may lessen in occurrence in individuals with former SARS-CoV-2 infection who have received subsequent vaccination against COVID-19. In a community survey of 28356 individuals aged 18 to 69 years with a history of prior SARS-CoV-2 infection, there was a significant reduction in symptoms of PASC after the first vaccine dose (12.8% decrease initially followed by 0.3% decrease per week) and second dose (8.8% decrease initially followed by 0.8% decrease per week) after receiving either mRNA or adenovirus vector COVID-19 vaccination. Thus, vaccination has the potential to reduce the global burden of PASC.[152]

CONCLUSIONS

Though the acute COVID-19 pandemic has proven to be one of the most catastrophic events of modern-day existence, PASC may prove to be an equally devastating and debilitating phenomenon threatening permanence. While researchers are starting to outline possible mechanisms of disease, large, longitudinal studies are needed to validate the pathophysiology of PASC and guide therapeutic strategies directed at both preventing PASC and curtailing symptom duration. Ongoing support and development of preventive vaccinations are warranted to reduce the incidence and severity of PASC symptoms. Proactive efforts to investigate and reduce the global impact of PASC will aid in understanding the mechanism of chronic postviral syndromes in hopes of mitigating future events akin to present day.

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Disclosures

K.B. Highland reports VielaBio, clinical trial for acute COVID. The other authors report no conflicts.

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