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REVIEW

Postural Orthostatic Tachycardia Syndrome in COVID-19: A Contemporary Review of Mechanisms, Clinical Course and Management

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Abstract: The long-term implications of COVID-19 have garnered increasing interest in recent months, with Long-COVID impacting over 65 million individuals worldwide. Postural orthostatic tachycardia syndrome (POTS) has emerged as an important component of the Long-COVID umbrella, estimated to affect between 2 and 14% of survivors. POTS remains very challenging to diagnose and manage – this review aims to provide a brief overview of POTS as a whole and goes on to summarize the available literature pertaining to POTS in the setting of COVID-19. We provide a review of available clinical reports, outline proposed pathophysiological mechanisms and end with a brief note on management considerations.

Keywords: POTS, COVID-19, long COVID, review

Introduction

Since its earliest descriptions, postural orthostatic tachycardia syndrome (POTS) has been known by many names – neuroasthenia, mitral valve prolapse syndrome and Da Costa's syndrome to name a few.[1] The current, most widely used definition of POTS was proposed by Schondorf and Law at the Mayo clinic in 1993.[2]

Since then, our understanding of POTS has improved with the emergence of a number of proposed pathophysiological mechanisms. Unfortunately, the nonspecific nature of symptoms in otherwise healthy young adults, often leads to a label of "functional" etiologies, for years before a diagnosis of POTS is made. Numerous therapies have been employed to mitigate the often-debilitating impact of this condition, with modest success at best.

Over the past few years, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), COVID-19 pandemic has had a profound impact on the world at large, resulting in nearly 700 million cases and 6.7 million deaths as of January 2023.[3] Following the initial ARDS-like syndrome, the long-term impact of COVID-19 is increasingly recognized. POTS has emerged as an important and debilitating piece of what is now broadly termed "Long-COVID". Diagnosis and management of POTS in these patients involves an added layer of complexity given the substantial clinical overlap of POTS with post-COVID symptoms.

In this review, we present an overview of POTS as a whole before focusing more specifically on POTS associated with COVID-19. We provide a comprehensive summary of available clinical reports and discuss the clinical nuances of POTS-COVID-19. We outline proposed pathophysiological mechanism and end with a brief note on management considerations overall, with a more specific focus on COVID-19.

Definition of POTS

POTS is defined as a sustained and disproportionate increase in the heart rate ≥ 30 beats/minute in adults or ≥ 40 beats/minute in adolescents (12–19 years), within 10 minutes of assuming an upright stance or head-up tilt. This must occur in

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the absence of orthostatic hypotension and without a clear alternative etiology. Importantly, these findings must be accompanied by clinical symptoms consistent with POTS for ≥ 6 months to make a definitive diagnosis.[4–6]

Clinical Features

POTS is characterized by a multitude of chronic symptoms that are clearly distinct from the associated orthostatic changes. Symptoms typically present between 15–50 years, with a mean age of onset at 30 years. A strong female preponderance (5:1) is reported - mostly in women of childbearing age.[7] The degree of functional impairment reported by young adults with POTS, approaches levels reported with congestive heart failure and chronic obstructive pulmonary disease, often translating into a very poor quality of life.[8]

Orthostasis-related symptoms include light-headedness or dizziness, palpitations, pre-syncope, a sense of weakness or heaviness (especially of the legs), tremulousness, shortness of breath, and chest pain.[7] Importantly, pre-syncope is not a common feature of POTS, encountered in less than a third of patients. Syncope is quite rare as well and should raise considerations of alternative diagnoses if predominant.[9]

A family history of orthostatic intolerance or tachycardia is reported in around 10% of subjects.[10] Episodes are frequently precipitated by heat, exercise, as well as a postprandial state. Other stressors including trauma, pregnancy, electrical injury, surgery, autoimmune disorders[11,12] and excessive psychosocial stress have also been reported.[7,9] Exacerbations of symptoms in the perimenstrual period is not uncommon. Episodes tend to be cyclical with symptoms ranging from weight fluctuations to changes in blood pressure and heart rate.[7,13]

Antecedent illness with viral infections of the upper respiratory and gastrointestinal tracts have been reported prior to onset of POTS.[2,14,15] Offending organisms identified include Epstein-Barr virus, Influenza and Borrelia burgdorferi.[16] It has also been associated with a number of autoimmune and connective tissue diseases such as Ehlers Danlos syndrome, rheumatoid arthritis, Hashimoto's thyroiditis, celiac disease and irritable bowel syndrome.

Gastrointestinal symptoms such as nausea, bloating, vomiting, diarrhea, constipation, abdominal pain also comprise a major part of the non-orthostatic symptoms seen in POTS.[17] From a neurological standpoint, most patients demonstrate subtle cognitive deficits commonly referred to as "brain fog", involving difficulty thinking, concentrating, and trouble remembering things or "a cloudy/fuzzy feeling in the head".[18–20] Other frequently reported symptoms include migraines, anxiety, fatigue, atypical chest discomfort, peripheral acrocyanosis, sleep disorders and exercise intolerance.[21]

The more recent 2020 Canadian Cardiovascular Society's writing committee has proposed a novel classification to better reflect the entire clinical spectrum of POTS.[22] These newer diagnoses incorporate terminologies such as POTS Plus, postural symptoms without orthostatic intolerance (PSWT), PSWT Plus and postural tachycardia of other cause (PTOC) in addition to the typical description of POTS. POTS Plus additionally includes non-cardiovascular symptoms such as gastric emptying disorders, severe constipation or diarrhea, neurogenic incontinence, severe chronic pain, joint hypermobility disorders, intractable headaches, anaphylactic symptoms, food intolerances and neurological sensory symptoms in addition to the typical orthostatic symptoms. Associated illnesses such as chronic migraines, cerebrospinal fluid leak syndromes, hypermobility disorders like Ehlers-Danlos syndrome, chronic fatigue syndrome, fibromyalgia, autoimmune disorders, mast cell activation disorders and celiac disease are frequently encountered. Similarly, patients with PSWT have the typical symptoms of orthostatic intolerance seen in POTS but do not meet the hemodynamic criteria. PSWT Plus syndrome includes a subset of patients with PSWT that have other non-cardiovascular symptoms and comorbid conditions similar to POTS Plus disorder. Another group of patients who do meet the hemodynamic criteria for POTS but have obvious underlying cause for the tachycardia can be categorized under PTOC. Common underlying conditions linked with this cluster of patients include acute hypovolemia, endocrinopathies, anemia, anxiety, medication side effects, recreational drug use and prolonged immobilization.[22]

POTS and COVID-19

Definition

The 2021 American Autonomic Society's statement on the definition of Long-COVID POTS reiterates the emphasis on all the symptoms seen post-COVID-19 such as breathlessness, palpitation, chest discomfort, fatigue, pain, cognitive

impairment, sleep disturbance, orthostatic intolerance, peripheral neuropathy symptoms, abdominal discomfort, nausea, diarrhea, joint and muscle pains, symptom s of anxiety or depression, skin rashes, sore throat, headache, earache and tinnitus when combined with excessive orthostatic tachycardia > 12 week post SARS-CoV-2 infection to make a diagnosis of POTS post-COVID-19.[5,23]

Proposed Mechanisms

Aside from the devastating pulmonary consequences of acute COVID-19 infection, the more chronic sequelae come under increasing scrutiny in recent months. "Long COVID" has been estimated to affect at least 10% of patients, translating to around 65 million individuals worldwide, though this is likely an underestimation.[24] It includes patients with ongoing symptomatic COVID-19 (4–12 weeks post infection) as well as those with Post-COVID-19 syndrome (>12 weeks post infection).[5] Broadly, Long-COVID encompasses a number of conditions including chronic fatigue syndrome, neurocognitive disorders, dysautonomia, myalgic encephalomyelitis and mast cell disorders to name a few.

A number of pathophysiological mechanisms have been proposed including, immune dysregulation leading to immune priming and autoimmune responses due to molecular mimicry (Figure 1). This is believed to potentially reactivate viruses such as EBV and HHV-6 which in turn negatively impact mitochondrial tissue energetics.[25,26]

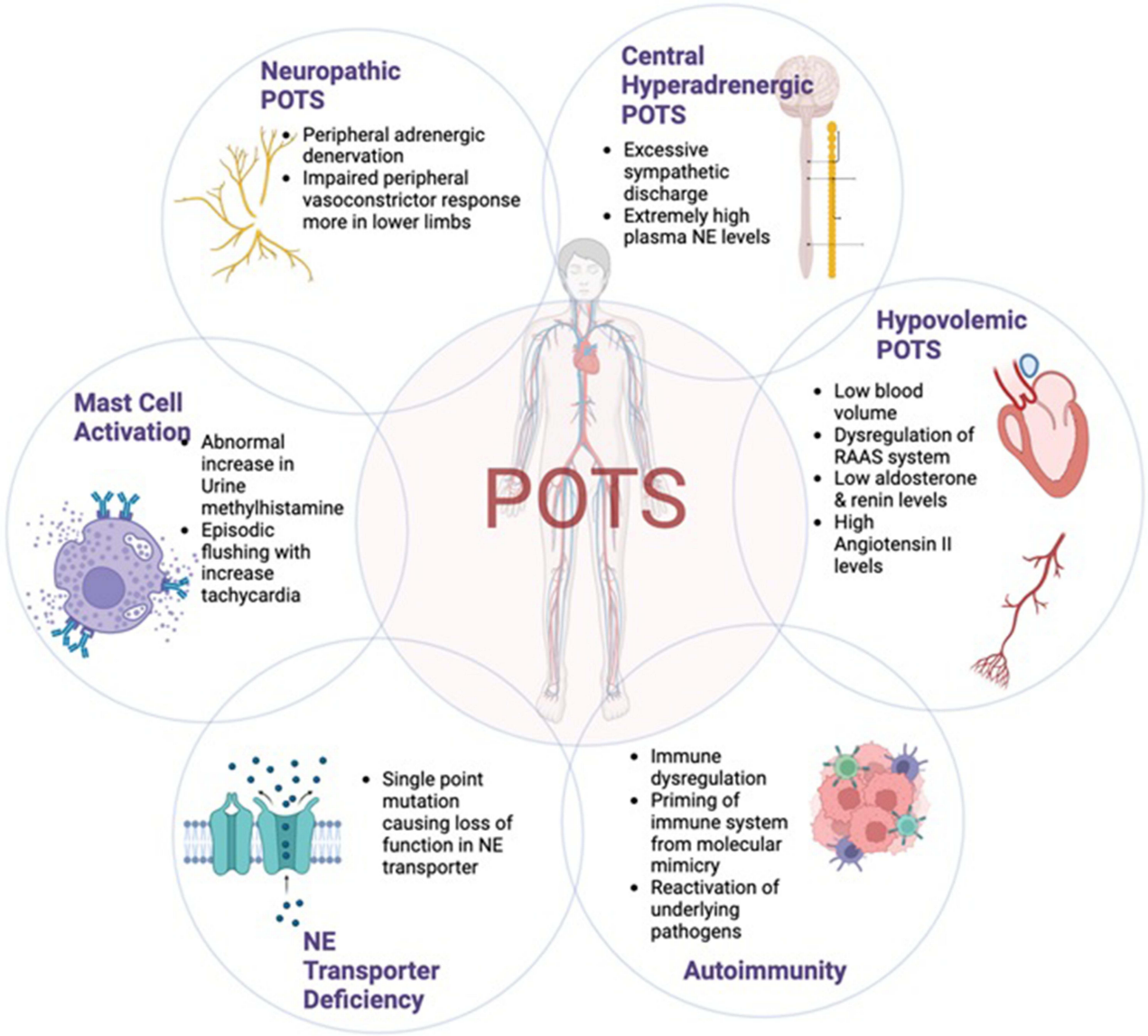

Figure 1 Proposed mechanisms and subtypes of POTS. Illustrative outline of the proposed mechanisms and subtypes of POTS in a COVID-19 and non-COVID setting.

Persistence of SARS-CoV2 viral particles in the gut, lymph nodes, hepatic tissue etc. has been proposed as a potential driver of immune changes related to long-COVID. In a study by Swank et al, circulating COVID spike protein antigens were noted in 60% of patients with long-COVID at 1 year post-infection.[27] A multitude of autoantibodies have been reported as potentially contributive to long-COVID, including those against ACE-2, adrenergic and muscarinic receptors as well as a sizeable number targeting extracellular proteins, coagulation factors and endothelial cells.[28] Li et al observed significantly elevated levels of α-1-adrenergic receptor autoantibodies, resulting in compensatory increase in α1AR vasoconstriction and βAR-mediated tachycardia.[29] Additionally, another study found that α2AR, β1AR, β2AR antibodies were not found in their POTS patient sera unless there was also expression of α1AR autoantibodies.[30]

To date, none of these antibodies have been definitively established to have a causative role.

More specific to POTS, adrenergic and muscarinic acetylcholine receptor autoantibodies, dysautonomia, small fiber neuropathies, platelet storage pool deficiencies, mast cell dysfunction with dysregulated histamine release as well as physical deconditioning have been implicated.[31] POTS has also been reported after COVID vaccination, though a definite causal relationship is yet to be established. Autoimmune mechanisms have once more been proposed given known rare off-target side effects such as neuropathies like Bell's palsy and myelitis etc. after mRNA vaccination. Given the integral nature of ACE receptors to the pathophysiology of COVID-19 (viral entry), ACE-2 antibodies which are highly represented in the cardiovascular system, could prove contributive as well.[32]

Prevalence

Accurately quantifying rates of post-COVID-19 POTS is challenging for a number of reasons. POTS is significantly underdiagnosed in the general population, even prior to the pandemic, making it very challenging to establish the diagnosis as truly new and related to COVID. With increasing awareness of the condition, without a detailed understanding as well as self-diagnosis on the rise, POTS is likely over diagnosed, in a bid to explain the rather nebulous symptoms of long-COVID. Furthermore, the diagnosis of POTS requires a degree of chronicity of symptoms (at least 3–6 months). A number of reports of "COVID-POTS" however are made much prior to this timeline and likely do not truly represent a diagnosis of POTS.

Recently a case series study of 20 patients post-COVID-19 infection reports that almost a third of patients experience frequent autonomic symptoms like dizziness, syncope, and palpitations within 6–8 months of acute infection.[16] Roughly 2–14% of survivors develop POTS, with another 9−61% who experience POTS-like symptoms within 6–8months.[33] In a recent study by Kwan et al, of nearly 300,000 individuals in the USA - rates of POTS were analyzed after both COVID infection and COVID vaccination.[34] They reported rates of POTS to be fivefold higher after COVID infection compared to vaccination (OR 5.35 vs 1.52).

Review of Clinical Reports

Contemporary literature indicates potential links between viral infections and vaccines (particularly HPV) with the development of POTS.[14,35,36] The earliest reports of a POTS-like syndrome in the aftermath of COVID-19 infection emerged in March 2020.[37] Since then, there has been growing awareness of a potential link between COVID infections and more recently vaccines and POTS. Table 1 outlines a list of case reports and case series on the topic.

In this review, all case studies and series (Jan 2020- Jan 2023) describing a relationship between COVID-19 and POTS are included. In terms of a timeline to onset of POTS, this was much earlier with post-mRNA vaccination POTS (1–8 weeks) rather than with Sars-CoV-2 infections (0–12 months). Notably, this must be interpreted with caution given the limited number of vaccine related POTS cases, as well as difficulty in precisely delineating post-vaccination symptoms. Furthermore, the symptoms observed were overall quite similar to those of POTS observed in a non-COVID setting. No particular unique or COVID-specific presentations of POTS were noted. There appeared to be a female predominance, characteristic of the general POTS population. Many patients also had a history of autoimmune diseases or dysautonomia symptoms. Severity of COVID infection did not appear to influence the severity of POTS symptoms or response to therapy. Though beyond the scope of our review, other studies report higher rates of POTS with mild infections due to higher numbers overall.[5,24] Majority of patients showed quite a marked improvement in symptoms with lifestyle measures, beta blockers, fludrocortisone and occasional ivabradine use. Anecdotal reports did note

Table 1 Overview of Clinical Descriptions of COVID-POTS

Author, Country (n)	Title	Time from Infection / Vaccine	Symptoms	COVID Severity	Therapy / Response
Reddy et al, (USA; n = 1)[38]	POTS secondary to the Messenger RNA COVID-19 Vaccine	7 days (Pfizer)	Sinus tachycardia, presyncope anxiety, sleep disturbances, and occasional numbness in the lower extremities	N/A	Lifestyle modifications – Good response
Park et al, (South Korea; n = 1)[39]	Transient POTS following COVID-19 vaccine	8 weeks (Moderna)	Intermittent headache, palpitation, fatigue, and dyspnea appearance one week after vaccination	N/A	Propranolol - near resolution at 5 months
Umapathi et al, (Singapore; n = 4)[40]	Acute hyperhidrosis and postural tachycardia in a COVID-19 patient	2–3 weeks (COVID)	Profound, intermittent bouts of sweating on his trunk and thighs; constipation, nausea and post-meal upper abdominal discomfort; marked tachycardia on standing and during passive 60-degree tilt without decrease in blood pressure	Moderate	Fludrocortisone, sodium tablets, pyridostigmine; symptom improvement
Rudofker et al, (USA; n = 3)[41]	An Exercise Prescription as a Novel Management Strategy for Long COVID	5 months (COVID), 1 month (COVID), 3 months (COVID)	Debilitating fatigue, lightheadedness, and brain fog, along with recurrent syncope with orthostasis; severe fatigue, lightheadedness, brain fog, and palpitations; dyspnea, coughing paroxysms, along with an increase in resting HR by 10–15 beats/min for any given work	Mild – 2/3 Moderate – 1/3	8-week prescription of recumbent/semi-recumbent exercise (rowing/biking) - marked symptom improvement for all three patients
Shouman et al, (USA; n = 27)[42]	Autonomic dysfunction following COVID-19 infection: an early experience	0–122 days, median: 7 (COVID)	Lightheadedness, orthostatic headache, syncope, hyperhidrosis, and burning pain; orthostatic symptoms without tachycardia or hypotension (41%); 22% postural tachycardia syndrome (POTS), and 11% had borderline findings to support orthostatic intolerance	Not specifically mentioned	Rehabilitative reconditioning and low dose beta blockers improved symptoms. Anxiolytics – no significant improvement. Gabapentin and topical lidocaine improved neuropathic symptoms for the small fiber/autonomic neuropathy subtype case; One patients with autoimmune autonomic ganglionopathy - relapse in symptoms following COVID-19 reinfection
Desai et al, (USA; n = 11)[43]	Autonomic dysfunction post–acute COVID-19 infection	39.5 ± 57.3 days (COVID)	Palpitations and fatigue, chest discomfort and/or dyspnea	Not specifically mentioned	Beta blockers (5; 4/5 improved), midodrine (1; improved), colchicine (1; unimproved), ibuprofen (2; improved), lifestyle modifications (2)
Agnihotri et al, (USA; n = 1)[44]	Autonomic neuropathy post-acute sequela of COVID-19	8 months (COVID)	Lightheadedness, palpitations, persistent hand and feet tingling and burning pain, hyperhidrosis, tremulousness, and dusky red discoloration of the feet on standing	Mild	Small dose of metoprolol, midodrine, and lifestyle modifications, which improved symptoms
Ocher et al, (USA; n = 1)[45]	Improvement in Hyperadrenergic Postural Orthostatic Tachycardia Syndrome (POTS) after COVID19 Infection	6 weeks (COVID)	Inappropriate sinus tachycardia	Moderate	Poor compliance metoprolol and ivabradine
Parker et al, (USA; n = 7)[46]	COVID-19 and postural tachycardia syndrome: a case series	21 ± 15 days (COVID)	Palpitations, dyspnea, and gastrointestinal complaints	Not specifically mentioned	6/7 did not respond to supportive therapy alone; 2 did not respond to ivabradine, midodrine and/or metoprolol; however 2/3 severely symptomatic patients responded to intravenous immunoglobulin

(*Continued*)

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Table 1 (Continued).

Author, Country (n)	Title	Time from Infection / Vaccine	Symptoms	COVID Severity	Therapy / Response
Hermel et al, (USA; n = 1)[47]	COVID-19 Vaccination Might Induce POTS	9 months (COVID) and 2 weeks (Pfizer)	Fatigue, brain fog, headache, sinus tachycardia, and dizziness	Mild	Lifestyle modifications, ivabradine, and dietary supplements to improve autonomic balance and minimize fatigue
O'Sullivan et al, (Ireland; n = 1)[48]	COVID-19-induced POTS treated with ivabradine	3 weeks (COVID)	Chest tightness, palpitations, dyspnoea and fatigue on mild exertion	Mild	First prescribed lifestyle modifications without symptom resolution, but significant improvement in symptoms 24 hrs. after treatment with ivabradine
Blitshteyn and Whitelaw, (USA; n = 20)[16]	POTS and other autonomic disorders after COVID-19 infection: a case series of 20 patients	6–8 months (COVID)	Fatigue, postural tachycardia, OI, dizziness, and exercise intolerance that were chronic and disabling	Not specifically mentioned	All prescribed lifestyle modifications, 16 (80%) required pharmacotherapy (beta blockers, fludrocortisone, midodrine, ivabradine, other medication for comorbid conditions); improvement with most patients, but only 3 (15%) had near/complete resolution of symptoms
Jamal et al, (USA; n = 24)[49]	Prospective Evaluation of Autonomic Dysfunction in Post-Acute Sequela of COVID-19	>3 months (COVID)	Poor exertional tolerance, tachycardia with minimal activity or positional change, and palpitations	2/24 – Moderate Remaining - Mild	N/A
Kitsou et al, (Norway; n = 1)[50]	Intermittent left bundle branch block with septal flash POTS in a young woman with long COVID	7 months (COVID)	Chest pain, functional dyspnoea, palpitations and an episode of syncope	Mild	Low-dose metoprolol; showed improvement 6 months after discharge
Johansson et al, (Sweden; n = 3)[51]	Long-Haul Post–COVID-19 Symptoms Presenting as variant POTS	4 months (COVID), 0 days (COVID), not mentioned	Profound exhaustion with associated sinus tachycardia; chest pain, fatigue, vertigo, headache; extreme fatigue, muscle weakness, insomnia, palpitations, and "brain fog" with trouble concentrating	Mild; severe; severe	Lifestyle modifications and ivabradine - some improvement; lifestyle modifications and propranolol but suspected concomitant mast cell activation syndrome lead to administration of H1 and H2 antihistamines - remains highly symptomatic; lifestyle modifications, pyridostigmine, and propranolol but suspected concomitant mast cell activation syndrome lead to administration of H1 and H2 antihistamines - despite up-titration of propranolol and pyridostigmine, still highly symptomatic
Varanasi et al, (USA; n = 1)[52]	Management of Long-COVID POTS With Enhanced External Counterpulsation	5 months (COVID)	Fatigue, "brain fog", shortness of breath, dyspnea upon exertion, aching chest	Severe	Enhanced external counterpulsation; marked improvement in symptoms 15 hour-long sessions
Kanjwal et al, (USA; n = 1)[53]	New-onset POTS Following COVID-19	4 weeks (COVID)	Fatigue, headache, dizziness, chest pain, and palpitations	Mild	Ivabradine and increased water/salt intake improved tachycardia but fatigue lingered
Rao et al, (USA; n = 3)[54]	Orthostatic and Exercise Intolerance in Recreational and Competitive Athletes With Long COVID	0 days (mRNA vaccine), 0 days (COVID), not mentioned	Fever, dyspnea, chest pain, intermittent exertional intolerance, and palpitations; decreased exercise tolerance and exertional chest pressure; severe fatigue, headaches, and palpitations that occurred predominantly in an upright position	Mild	Lifestyle modifications and recumbent exercise - significant improvement; pyridostigmine and supine exercise with good results; recumbent exercise with some improvement in symptoms

Sanada et al, (Japan; n = 1)[55]	Overlapping Myocarditis and POTS After COVID-19 Messenger RNA Vaccination: A Case Report	2 weeks (Pfizer)	Severe fatigue, headache, and orthostatic symptoms including lightheadedness and palpitations.	N/A	Lifestyle modifications, propranolol, midodrine, and droxidopa treatment led to symptom improvement; myocarditis treated with IVIG
Miglis et al, (USA; n = 1)[56]	A case report of POTS after COVID-19	4 months (COVID)	Tachycardia (standing HR of 150 bpm after showering), chest pains, shortness of breath, fatigue and exercise intolerance, along with subjective fevers and insomnia	Moderate	Propranolol prescribed with some improvement but not complete resolution of symptoms
Ishibashi et al, (Japan; n = 1)[57]	Post-COVID-19 POTS	3 weeks (COVID)	Fatigue, feeling unwell, intermittent palpitation, dyspnea and chest pain	Not specifically mentioned	Low-dose bisoprolol(marked improvement in symptoms)
Kalia et al, (USA; n = 1)[58]	Post-COVID-19 Syndrome: A Novel Diagnosis	3 months (COVID)	Tachycardia, headaches, and near syncopal events	Not specifically mentioned	Metoprolol; showed near resolution of symptoms
Bosco and Titano, (Israel; n = 1)[59]	Severe Post-COVID-19 dysautonomia: a case report	3 months (COVID)	Worsening post-exertional fatigue, slowed cognition with increased forgetfulness and difficulty concentrating, headaches, blurred vision and generalized body aches and weakness; palpitations	Mild	Lifestyle modifications and recumbent exercises; some improvement in symptoms but still unable to return to work

Note: Disease severity: Mild: Not hospitalized; Moderate – Hospitalized (Non-ICU); Severe – ICU hospitalization.

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significant improvement with IVIG and EECP use – albeit much larger studies are needed before any conclusions can be made.

Diagnosis

The diagnosis of POTS is extremely challenging and mandates a meticulous approach. Highlighting this is a study by Shaw et al, reporting that 4 in 5 patients are diagnosed with psychiatric or psychological conditions prior to ultimately receiving a diagnosis of Post-COVID POTS.[19] Notably, only 37% of these patients go on to retain their psychiatric diagnosis once POTS is diagnosed.

The nonspecific nature of symptoms compounded by the near ubiquity of tachycardia contributes to the difficulty in diagnosis. Symptomatology is integral to the diagnosis of POTS and must occur in concordance with the defined orthostatic changes. Focus solely on symptoms or on orthostatic changes can lead to misdiagnosis. Important differentials include, dehydration with associated orthostasis, neural-reflex syncope, inappropriate sinus tachycardia, phaeochromocytoma, psychiatric conditions, and often under-recognized medication related side effects.[31]

The 2015 HRS expert consensus statement recommends beginning with a thorough clinical history and physical examination along with orthostatic vitals and a 12-lead electrocardiogram. The initial visit should focus on defining the problem and ruling out alternative diagnoses. Associated conditions, likely stressors and triggers, the severity of the clinical symptoms and factors that worsen or improve a patient's QOL must be defined. A special focus on diet (salt/water intake), functional capacity and an in-depth review of the autonomic system is critical. An important but often overlooked part of the clinical history is a thorough review of medications including substance use that could exacerbate or mimic POTS. Antihypertensives, stimulants and antipsychotic drugs are particularly noteworthy in this regard. An algorithmic approach to diagnosis is outlined in Figure 2.

Laboratory tests such as complete blood count, electrolytes, renal function tests, thyroid function test, ferritin and morning cortisol levels should be done in the initial visit to rule out more common differentials.[60] These include hyperthyroidism, infection, dehydration, pheochromocytoma etc.

Several overlapping mechanisms are shared between POTS and inappropriate sinus tachycardia. Use of a 24-hour Holter monitoring system could help differentiate the two. Most patients with suspected POTS might not have the classic

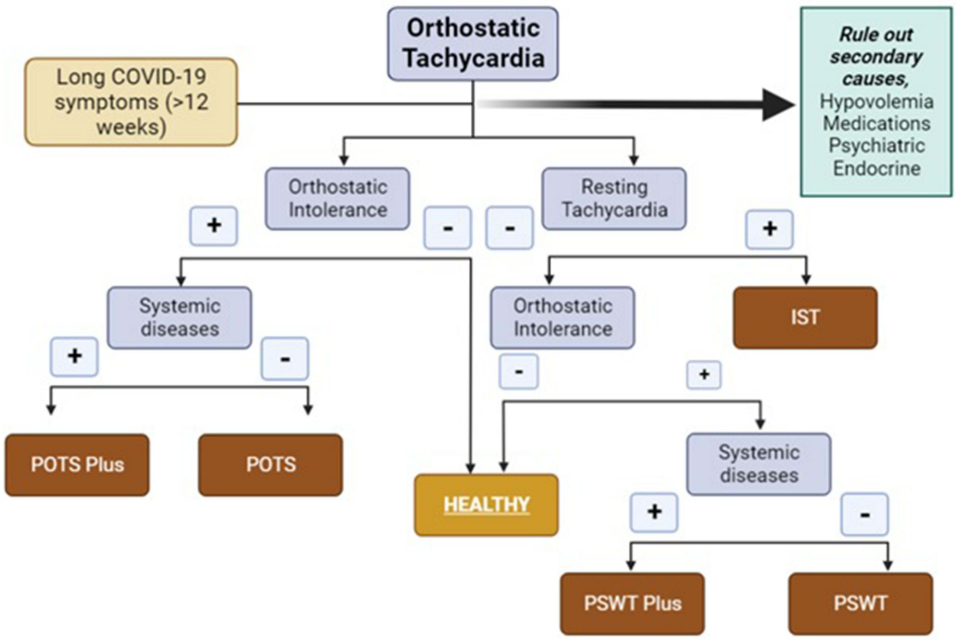

Figure 2 Algorithmic approach to diagnosis of POTS. Schematic diagram outlining a diagnostic approach to POTS. Adapted from the HRS 2015 guidelines and CCS position statement 2020.[4,22]

Abbreviations: PSWT, Postural symptoms without orthostatic intolerance; POTS, Postural orthostatic tachycardia syndrome; IST, Inappropriate sinus tachycardia.

30-point increase in HR during their clinic visit and may instead exhibit a trend towards increased HR on standing. Such patients may benefit from a monitoring device that can help distinguish these patterns from other arrhythmias.[61] Given that heart rate varies fluctuates diurnally, morning assessments are usually found to be more sensitive.[62]

A head-up tilt test or an active standing test can also aid in diagnosis.[63] A 30-beat-per-minute increase in heart rate within the first 10 minutes of head-up tilt or active standing test without concomitant blood pressure decrease and with reproduction of symptoms is diagnostic of POTS.[63]

Autonomic testing is not routinely performed unless there is a very high suspicion for autonomic neuropathy. In those instances, referral to a specialist may be necessary. Autonomic testing includes a cascade of tests which include Valsalva maneuvers, deep breathing tests, tilt table testing, thermoregulatory sweat test and sudomotor axonal reflex tests along with serum levels of antinicotinic ganglion antibodies, plasma norepinephrine levels and a 24-hour urinary sodium. The clinical utility of neuroimaging studies or antibody testing is unclear in these patients and currently has no role in routine clinical practice.[22]

Treatment

An individualized approach is essential in the management of POTS and is primarily directed at symptom mitigation in an effort to improve quality of life. The initial focus of therapy is directed at non-pharmacological therapies. An overview of available treatment options is provided in Table 2.

Non-Pharmacological Therapies

Volume optimization is integral to management, as upto 70% of POTS patients are reported to be hypovolemic (approximately 13% volume deficit on average).[64] This is achieved by encouraging oral hydration (3–4liters/day) and use of compression stockings (thigh-high) as well as abdominal binders to increase intravascular circulating blood volume. Salt supplementation (10g/d) is also recommended with the same goal in mind. Use of salt tablets, addition during cooking or intake of high salt foods are all acceptable options and are left to patient preference.

Exercise training has proven quite effective overall in improving physical conditioning, soleal muscle pump functioning as well as quality of life.[65] Exercise prescriptions have proven effective in COVID-POTS. In particular, recumbent/semi-recumbent exercises such as rowing or cycling are favored in these patients.[41] A graded program is

Table 2 Overview of Management of POTS

Non-Pharmacological	First Line Pharmacological Agents	Second Line / Experimental Agents
Volume optimization: • Oral hydration • Salt supplementation • Compression stockings • Abdominal binders	**Lowering Heart Rate**: • Beta blockers (Propranolol) • Ivabradine • Pyridostigmine	**Supplements**: • Iron • Vitamin D • Alpha lipoic acid
Exercise training (Recumbent preferably) – Rowing / cycling	**Volume expansion**: • Fludrocortisone	Droxidopa
Small meals / Avoid dehydration or excess alcohol	**Vasoconstriction**: • Midodrine	Desmopressin
	Sympatholytics / Stimulants: • Clonidine • Alpha-methyl dopa • Modafinil	Enhanced extracorporeal counter pulsation therapy (EECP)
		IVIG
		Cardiac Neuromodulation

Note: Italicized therapies are non-guideline recommended options.

recommended with a slow up titration of intensity and duration. It is important to counsel patients that symptoms frequently worsen initially before subsequent improvement. A minimum of three months of exercise therapy is recommended before judging the efficacy of the regimen.[66,67]

Anecdotal reports indicate a potential utility of enhanced extracorporeal counter pulsation therapy (EECP), though more large scale data is required.[52]

Pharmacological Therapies

Medications are initiated if lifestyle measures prove insufficient and are directed at specific pathophysiological targets. Given the heterogenous nature of POTS and varied range of proposed mechanisms in different patients, efficacy of these agents is similarly variable.

Beta blockers such as propranolol are particularly favored in hyperadrenergic forms of POTS. Pre-emptive administration prior to exercise has been reported to be effective in improving exercise capacity.[63] A small trial of 19 patients by Fu et al, found exercise training to be equivalent to propranolol in terms of improving quality of life and restoring hemodynamics.[68] Ivabradine (I-funny current; If blocker) acts selectively on the SA node to lower resting heart rates. It has been used off-label in patients with POTS and is reported to improve quality of life and reduce resting heart rates.[69,70] Pyridostigmine (an acetylcholinesterase inhibitor) has been used with some benefit, particularly in patients with autoimmune / paraneoplastic POTS. Though patients did report modest clinical benefit, this was offset by significant gastrointestinal side effects.[71]

In addition to the aforementioned oral hydration and salt intake, pharmacological volume expansion with fludrocortisone (mineralocorticoid agonist) has been found beneficial in a number of patients. It is important to monitor for hypokalemia with prolonged use.[72] Midodrine (Alpha agonist) is also recommended per the HRS guidelines, particularly in the neuropathic subtype of POTS. It acts by promoting vasoconstriction, thus minimizing postural hypotension. Chronic use is avoided given concerns related to long-term sympathetic activation.[73]

A number of other agents including droxidopa (Norepinephrine precursor), Desmopressin, erythropoietin, Modafinil, Clonidine, Methyldopa, iron and vitamin D supplementation as well as alpha lipoic acid have been used with varied success. Data to support their use is however quite limited.

Extensive concerns for an immunological contribution to the pathophysiology of POTS, has prompted interest in immunomodulatory therapies – namely IVIG.[74] This is of particular interest in the setting of COVID-19, where immunological dysregulation is believed to play a key role. A review of ongoing clinical trials for POTS in patients with COVID-19 is outlined in Table 3.

Table 3 Ongoing Clinical Trials on POTS in COVID-19

Title	Country	NCT	Status	Description
Efficacy and Safety Study of Efgartigimod in Adults with Post-COVID-19 POTS (POTS)	USA	NCT05633407	Recruiting	Testing safety and efficacy of efgartigimod in treating post-COVID POTS
Physical Training in Patients with POTS After Covid-19 (POTS-ReCOV)	Sweden	NCT05094622	Recruiting	Studying the efficacy of an exercise treatment plan for those with long COVID POTS symptoms
Post-COVID-19 Outpatient Care and Biomarkers (POSTCOV)	Austria	NCT05398952	Recruiting	Study post-acute sequelae of COVID-19 by establishing a blood biobank, examining circulating biomarkers and ncRNAs, testing cfDNA in plasma and serum, and establishing correlations between ncRNAs and cfDNAs
Ivabradine for Long-Term Effects of COVID-19 With POTS Cohort	USA	NCT05481177	Not Yet Recruiting	Study of ivabradine efficacy in reducing heart rate for those with long COVID POTS
Cardiovascular Autonomic and Immune Mechanism of Post COVID-19 Tachycardia Syndrome	USA	NCT05421208	Recruiting	Determine inflammatory and immune profile of post-COVID POTS; measure peripheral nervous system activity using heart rate variation, and use the COMPASS-31 test to assess autonomic symptoms

COVID-Specific Considerations

The ongoing pandemic has brought much awareness to millions of patients and providers regarding the existence of POTS. This has undoubtedly been a positive step with regards to earlier diagnosis and initiation of treatment as well as increased interest in research towards this condition. On the other hand, however, there is also a significant risk of overdiagnosis / self-diagnosis. Given the largely nonspecific yet debilitating nature of symptoms encountered with long-COVID, POTS could serve as an easy "diagnostic" label to a frustrated patient. It is hence essential that prior to establishing a diagnosis of POTS, a detailed evaluation is performed and more sinister differentials are ruled out. Importantly, chronicity is an integral component of the diagnosis – a large proportion of case reports and case series however report a diagnosis of POTS well before the defined 6-month symptom window.

Going forward, more work is needed to outline the natural history of POTS in the setting of COVID-19 and determine if this timeline requires a change or if this is just a testament to overdiagnosis. Given the marked improvement observed in a majority of patients, research is required to better delineate the difference between post-COVID symptoms and true POTS. This is particularly intriguing given the much more modest responses to therapy in non-COVID settings, which once more raises the question of whether the condition described is truly POTS or if varied pathophysiology in a COVID setting renders it more amenable to conventional therapies.

Conclusion

At this point, it is clear that POTS is a part of the umbrella of Long-COVID and is encountered after COVID-19. Future work is needed to accurately define the true prevalence / pathophysiology and clinical behavior of POTS in this setting as well as the impact of different viral variants. Integral to this is to verify accurate diagnosis of patients, without which the diagnosis loses any therapeutic utility. Widespread education of healthcare providers regarding the intricacies of this condition and establishment of tertiary care centers of excellence are integral. Greater resource allocation is needed to improve access to these specialists and to train allied health personnel to aid in this pursuit. The use of telemedicine in a technologically proficient young population could aid in more effective delivery of care.

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