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The possible association between COVID-19 and postural tachycardia syndrome

David S. Goldstein, MD, PhD

From the Autonomic Medicine Section, Clinical Neurosciences Program, Division of Intramural Research, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland.

Coronavirus disease 2019 (COVID-19), the illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), involves other body organs besides the lungs. In recovered patients, post-acute sequelae of COVID-19 may include dysautonomia, in which changes in functioning of $\geq$1 components of the autonomic nervous system (ANS) adversely affect health. This viewpoint focuses on the dysautonomia postural tachycardia syndrome (POTS).

POTS is characterized by a sustained heart rate increment of $\geq$30 beats/min within 10 minutes of standing or head-up tilt. Cardiologic symptoms include chest pain, palpitations, exercise intolerance, and orthostatic intolerance.

Other symptoms may include fatigue, "brain fog," gastrointestinal issues (e.g., abdominal pain, bloating, gastroparesis, and nausea), chronic pain (e.g., headache, temperomandibular joint disorder, and fibromyalgia), and sleep abnormalities. Comorbidities include Ehlers-Danlos syndrome, mast cell activation syndrome, sensory neuropathy, or autoimmune disorders (e.g., lupus and Sjogren syndrome). These aspects extend beyond cardiology.

Both post-acute sequelae of COVID-19 and POTS manifest as multi-system, multi-disciplinary syndromes. Thinking in terms of the "extended ANS" (EAS) may help comprehend how these syndromes come about and how to test for and treat them.[1]

EAS

The ANS has been defined by 3 components: the sympathetic nervous system, the parasympathetic nervous system (PNS), and the enteric nervous system. The EAS expands the meaning of "autonomic" in 2 ways, neuroendocrine and neuroimmune.

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Cannon taught that activation of the sympathetic nervous system and adrenal gland in emergencies helps maintain *homeostasis*, a word he invented. Since then, other neuroendocrine systems have been described that are closely linked to components of the ANS. These include the hypothalamic-pituitary-adrenocortical (HPA) system, the renin-angiotensin-aldosterone system (RAS), and the arginine vasopressin system. Across a variety of stressors, responses of plasma epinephrine (EPI) levels are more closely tied to those of adrenocorticotropin (the anterior pituitary hormone of the HPA axis) than of norepinephrine (NE, the neurotransmitter of the sympathetic noradrenergic system (SNS)). These findings support a close association between the sympathetic adrenergic system (SAS) and the HPA axis. The SNS and SAS in turn are closely connected to the RAS. Occupation of β_1 adrenoceptors in renal juxtaglomerular cells releases renin, adrenomedullary chromaffin cells possess angiotensin receptors that when occupied evoke EPI secretion, and there is a central neural renin-angiotensin system that participates in the regulation of sympathetic outflow. Angiotensin-converting enzyme type 2 converts angiotensin II (AII) to angiotensin 1–7, which opposes the effects of AII. SARS-CoV-2 enters cells via binding to angiotensin-converting enzyme type 2. In addition to being a pressor and the body's main water-retaining hormone, in the brain vasopressin augments baroreflexive restraint of sympathetic outflows.

A second aspect of the EAS is neuroimmunity. Cortisol is well known to be the major anti-inflammatory compound of the HPA axis. The cytokine interleukin 6 activates the HPA axis[2] and stimulates the production of aldosterone, demonstrating links between the immunological and neuroendocrine facets of the EAS. A cholinergic anti-inflammatory pathway involves cytokine-induced increases in vagal afferent traffic and vagal efferent inhibitory effects on inflammasomal cytokine release.[3] Vagal stimulation inhibits the production of the cytokine tumor necrosis factor α, probably via the 2 main neurotransmitters of the ANS, acetylcholine and NE. No simple concept explains catecholaminergic influences on immunity. Although across a variety of stressful situations increases in EPI levels are associated with elevations of interleukin 6, bases for this relationship are poorly understood. Immune cells synthesize and release catecholamines,[4] but the functional significance is unknown.

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Stress and the central autonomic network

In the 1990s Chrousos and Gold proposed the existence of a stress syndrome elicited by activation of the "central stress system." A recently proposed schema[1] embeds this system within the "central autonomic network."[5] The central autonomic network is the source of outflows to ANS components including the SNS, SAS, and PNS. When the central stress system is activated, PNS outflows generally decrease, which would be expected to promote tachycardia. Other manifestations of PNS inhibition include decreased gastrointestinal motility, decreased salivation and lacrimation, and decreased urinary bladder tone.

Potential pathophysiological mechanisms of post-COVID POTS

Acute COVID-19 is associated with several central nervous system abnormalities including stroke, encephalopathy, encephalitis, anosmia, anorexia, headache, nausea, and delirium. A meta-analysis of the literature from previous epidemics (SARS and Middle East respiratory syndrome) noted high frequencies of confusion, depressed mood, anxiety, impaired memory, and insomnia.[6] Conversely, patients with POTS often report a recent viral illness.[7]

There are several pathophysiological mechanisms that might be associated with post-COVID POTS. They are not mutually exclusive, and to date there is no published evidence supporting any of them. One mechanism is hypovolemia. Fever, anorexia, nausea, excessive nocturnal sweating, and prolonged bed rest might operate together to decrease blood volume and secondarily increase cardiac SNS outflow. In POTS, deconditioning can be part of a vicious cycle involving low stroke volume, high SNS or SAS outflows, exercise intolerance, and fatigue. These findings have been called "Grinch heart."[8]

Second, SARS-CoV-2 might infect and destroy extracardiac postganglionic SNS neurons, secondarily increasing cardiac SNS outflow in a manner analogous to neuropathic POTS. This might include splanchnic venous pooling or a failure of reflexive mesenteric vasoconstriction during orthostasis.

Third, SARS-CoV-2 could invade the brainstem and alter functions of medullary centers, resulting in increased central sympathetic outflows in a manner analogous to *takotsubo* cardiopathy.[9] Centrally mediated increases in sympathetic noradrenergic and SAS outflows as part of stress system activation might be associated with psychiatric morbidity such as anxiety or depression. There could be alterations in brain perfusion manifesting with "brain fog."

Fourth is autoimmunity. In response to a viral infection, immune responses targeting the virus are regulated in a complex, dynamic way, balancing attacking the virus vs attacking the host's own cells. There is substantial literature describing autoimmune markers and autoantibodies in POTS; however, there is insufficient evidence of pathogenicity. Considering the survival advantage of molecular mimicry by a virus and the novelty of COVID-19, POTS could result from disruption of this delicate balance—"dyshomeostasis."[1]

First case report of COVID-associated POTS

The first reported patient with COVID-associated POTS[10] awoke with palpitations and shortness of breath on day 7 of her acute illness. On day 22 she noted hyperactivity, pressured speech, and a feeling of inner restlessness and on day 24 episodic "adrenaline surges" characterized by diarrhea, tremors, and worsening restlessness. On day 45 she had episodic facial flushing, dermatographia, and nonpruritic hives. She tested negative for SARS-CoV-2 and underwent formal ANS evaluation. The testing confirmed excessive orthostatic tachycardia, normal or even exaggerated increases in blood pressure in late Phase II and Phase IV of the Valsalva maneuver, and large pressure oscillations without hyperventilation during 10 minutes of head-up tilting. Plasma NE with the patient supine was normal at 379 pg/mL and was 310 pg/mL when she was upright (time upright not reported). The workup was insufficient to identify hypovolemia, sympathetic noradrenergic neuropathy, increased SAS outflow, or autoimmunity as pathophysiological mechanisms.

Autonomic function testing that applies the EAS concept would include evaluations not only of Langley's ANS but also of the neuroendocrine component (SAS, HPA axis, RAS, and vasopressin) and the neuroimmune component (both humoral and cellular). COVID-19 represents a unique opportunity to understand mechanisms of postinfectious autonomic syndromes involving the circulation.

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