Autonomic dysfunction and postural orthostatic tachycardia syndrome in post-acute COVID-19 syndrome

Artur Fedorowski[1,2] and Richard Sutton[2,3]

[1] Department of Cardiology, Karolinska University Hospital, and Department of Medicine, Karolinska Institute, Stockholm, Sweden
[2] Department of Clinical Sciences, Lund University, Malmö, Sweden
[3] Department of Cardiology, Hammersmith Hospital, National Heart & Lung Institute, Imperial College, London, UK

Corresponding author: Dr. Artur Fedorowski, MD, PhD, Assoc. Prof.
Department of Cardiology, Karolinska University Hospital,
Eugeniavägen 23, 171 64 Solna, Sweden.
Email: artur.fedorowski@ki.se

Post-acute-sequelae of COVID-19 present major problems for many patients, their physicians, and healthcare system. They are unrelated to severity of the initial infection, often highly symptomatic and can follow vaccination. Many sequelae are cardiovascular dysautonomic with Postural Orthostatic Tachycardia Syndrome in 30%. Prognosis is unknown and treatment is still unsatisfactory.

When the COVID-19 pandemic swept around the world in early 2020, few could imagine the long-term consequences of this disease. During the first pandemic year, pre-vaccination, the focus was on surviving the acute infection, which many, especially among older patients, failed. In summer 2020, a new group of patients, so called post-COVID long-haulers, emerged. Constantly tired, incapable of work, predominantly young/middle-aged women, with multiple symptoms, including palpitations, fast heart, orthostatic and exercise intolerance, and chest pain dominating[1]. Many physicians, cardiologists, and neurologists, in particular, realized that some symptoms were identical to those of postural orthostatic tachycardia syndrome (POTS) as also were patients' responses to cardiovascular (CV) autonomic tests[2]. Other variants of CV autonomic dysfunction such as inappropriate sinus tachycardia followed[3]. POTS is considered to be a major phenotype in the new post-acute COVID-19 syndrome (PACS) with estimated prevalence ~30% among very symptomatic patients[4], but other forms of CV dysautonomia such as orthostatic intolerance/hypotension and vasovagal reflex susceptibility have been also reported[5].

POTS cannot be confirmed without correctly interpreted CV autonomic testing. An appropriately performed active standing test (ideally with beat-to-beat non-invasive blood pressure [BP] recording as POTS criteria may be transient) is sufficient but often omitted or its results ignored. The syndrome includes exaggerated chronotropic response to standing of >30 bpm with maintained BP, chronic symptoms of orthostatic intolerance and fatigue, in absence of other explanatory pathologies[6]. The whole picture is usually complicated by other complaints including unexplained chest pain, migraine, brain fog, muscle weakness, and sleep disturbances[7] (Fig. 1). This pattern may force a patient to wander between various specialties unable to procure a diagnosis which leads to available therapy delivered by a caring medical team, including exercise, support stockings, fluids, ivabradine for tachycardia, and midodrine to support BP.

Recent reports have appreciated this problem by underscoring the place of POTS in the post-COVID landscape[1] calling for more diagnostic vigilance, greater availability of healthcare resources and new therapeutic options. Interestingly, POTS and related conditions, such as mast cell disorders, chronic fatigue, and general dysautonomia are diagnosed more often within 3 months following COVID-19 infection but may also develop after COVID-19-vaccination. The medium to long-term prognosis has been little studied as yet[8]. A recent report suggests that many over 12 months may spontaneously recover[9].

As both SARS-CoV-2 infection and COVID-vaccines may trigger POTS and other CV dysautonomias, a question has been raised whether these factors may be potent immune triggers evoking an autoimmune response in susceptible individuals. Moreover, the occurrence of these cardiovascular dysautonomias seems unrelated to the severity of initial infection[4]. Future research may reveal an immunomodulating agent that abates the hypothetically overstimulated/misdirected immune response. However, reliable

immunological tests capable of identifying the immune mediator of the observed functional changes in the autonomic nervous system are currently lacking. Additionally, identification of genetic and epidemiologic markers of increased cardiovascular dysautonomia risk should be targeted.

The post-COVID cardiovascular autonomic dysfunction may affect global circulatory control producing not only a POTS like pattern but also tachycardia at rest, BP instability with both hypo- and hypertension, and local circulatory disorders as in migraine, coronary microvascular dysfunction, or Raynaud-like symptoms (Fig. 1). Microvascular dysfunction with inadequate regional micro- and macrovascular responses such as vasospasm and circulatory mismatch between local oxygen demands and supply, and venous retention leading to pooling and reduced venous return on standing may explain the plethora of symptoms, frequently observed in POTS. There are sparse reports suggesting microvascular dysfunction to be an important mechanism of post-COVID complications[10]. All these dysautonomic phenotypes may coexist, and, more importantly, they preferentially affect young/middle-aged women, suggesting genetic predisposition and possible sex hormone role. POTS is extremely rare among prepubertal and postmenopausal women[6].

As more evidence emerges, it will be important to have better precision of POTS phenotyping in prospective PACS cohorts, to identify reliable disease biomarkers, and to design clinical trials with best candidates for an effective therapy of the syndrome.

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Competing interests

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Figure legend.

Typical manifestations of post-acute COVID-19 syndrome (PACS)-related cardiovascular autonomic dysfunction. Two major types of cardiovascular autonomic dysfunction, global and local, usually overlap. Postural orthostatic tachycardia syndrome and inappropriate sinus tachycardia are the most prevalent phenotypes found in ~30% of highly symptomatic PACS patients. Peripheral circulatory disorders are believed to stem from microvascular and endothelial dysfunction and may lead to local symptoms such as headache, cognitive impairment ("brain fog"), chest pain (angina-like), dyspnea, heat/cold intolerance, Raynaud-like phenomena, and venous pooling. A relative and absolute hypovolemia may be present.

Fig. 1