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Post-COVID-19 Tachycardia Syndrome: A Distinct Phenotype of Post-Acute COVID-19 Syndrome

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ABSTRACT

In this paper we highlight the presence of tachycardia in post-acute COVID-19 syndrome by introducing a new label for this phenomenon—post-COVID-19 tachycardia syndrome—and argue that this constitutes a phenotype or sub-syndrome in post-acute COVID-19 syndrome. We also discuss epidemiology, putative mechanisms, treatment options, and future research directions in this novel clinical syndrome.

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KEYWORDS: COVID-19; Inappropriate sinus tachycardia; Postural orthostatic tachycardia syndrome; Tachycardia

INTRODUCTION

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has triggered a pandemic of coronavirus disease 2019 (COVID-19) lasting for more than 1 year, with over 130,000,000 reported cases globally as of April 2021.¹ Due to its novelty and lack of historical data, several aspects of COVID-19 remain unclear. So far, COVID-19 research mostly focused on epidemiology, risk factors for disease severity, description of the clinical course, and identification of optimal management strategies in hospitalized COVID-19 patients.

However, there is growing evidence that COVID-19 may cause persistent symptoms and organ damage that stretch beyond the 3-month period after the infection, usually regarded as the normal convalescence phase. This is now considered to constitute a novel clinical long-term condition: post-acute COVID-19 syndrome.² The clinical characteristics, pathophysiology, and appropriate management strategies for post-acute COVID-19 syndrome remain largely unknown.

Patients with post-acute COVID-19 syndrome have a wide range of symptoms including fatigue, chest pain, reduced exercise tolerance, cognitive impairment, dyspnea, fever, headache, and loss of smell and taste, but rapid heartbeats and palpitations are typical and frequent complaints.³ We have recently reported that a sub-group of patients with post-acute COVID-19 syndrome develop postural orthostatic tachycardia syndrome, a cardiovascular dysautonomia associated with sinus tachycardia and intolerance following orthostatic challenge.⁴ However, postural orthostatic tachycardia syndrome is likely not the sole explanation for elevated heart rate; several other conditions may

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explain tachycardia in post-acute COVID-19 syndrome, for example, inappropriate sinus tachycardia, deconditioning, hypoxia, anxiety, sinus node dysfunction, myocarditis/heart failure, and persistent fever.

In this paper we highlight the presence of tachycardia in post-COVID-19 patients with persisting symptoms by introducing a new label for this phenomenon: post-COVID-19 tachycardia syndrome, and argue that this should be considered a phenotype or sub-syndrome in post-acute COVID-19 syndrome. Furthermore, we discuss the epidemiology, putative mechanisms, treatment options, and future directions for clinical and basic research in this novel clinical syndrome.

POST-ACUTE COVID-19 SYNDROME

Post-acute COVID-19 syndrome is defined as symptoms after COVID-19 infection persisting for 4-12 or >12 weeks.² The prevalence of post-acute COVID-19 syndrome remains difficult to establish and varies by definition and methodology used. A recently published structural follow-up of Swedish health care workers with mild COVID-19 documented a post-acute COVID-19 syndrome prevalence of 10%.⁵ The longest follow-up study to date of hospitalized patients reports that >60% suffer fatigue or muscle weakness at 6 months follow-up.³ Given the extremely high number of reported cases and the uncertain long-term prognosis, post-acute COVID-19 syndrome is likely to become a major clinical problem for the foreseeable future.

Unfortunately, post-acute COVID-19 syndrome remains a poorly defined clinical syndrome. Typical symptoms include headache, fatigue, dyspnea, and mental blurring, but a very extensive list of symptoms reflecting involvement of multiple organs have been reported. Moreover, the type of symptoms reported may differ vastly among individuals with post-acute COVID-19 syndrome. In addition, symptoms are likely to be caused by several different mechanisms. All of this taken together suggests that post-acute COVID-19 syndrome should not be considered a single clinical syndrome but rather a uniting term characterized by different sub-syndromes and phenotypes.⁶

POST-COVID-19 TACHYCARDIA SYNDROME AS A SUB-SYNDROME OR PHENOTYPE OF POST-ACUTE COVID-19 SYNDROME

In our experience, approximately 25%-50% of patients at a tertiary post-COVID multidisciplinary clinic report tachycardia or

palpitations persisting 12 weeks or longer. Systematic investigations suggest that 9% of post-acute COVID-19 syndrome patients report palpitations at 6 months.³

We and others have recently presented case reports describing patients with postural orthostatic tachycardia syndrome associated with post-acute COVID-19 syndrome.^{4,7} This syndrome is characterized by sinus tachycardia and

symptoms of orthostatic intolerance. Inappropriate sinus tachycardia can also be triggered by infections (and associated conditions) and shares some clinical features with postural orthostatic tachycardia syndrome.⁸ Importantly, apart from the evident tachycardia, both these conditions are characterized by other non-specific symptoms such as headache, fatigue, and cognitive impairment, resembling symptoms reported in post-acute COVID-19 syndrome.

Moreover, Holter electrocardiogram (ECG) monitoring and measures of heart rate during different physiological challenges may not correlate to reported symptoms in post-acute COVID-19 syndrome, that is, patients with and without abnormally elevated heart rate may share several symptoms and there is no typical symptom strongly linked to the presence or absence of tachycardia in post-acute COVID-19 syndrome.

Together, this suggests that tachycardia is a common feature in post-acute COVID-19 syndrome and it may clinically present as postural orthostatic tachycardia syndrome or inappropriate sinus tachycardia. We suggest that persistent symptomatic tachycardia may be a sub-syndrome or specific phenotype of post-acute COVID-19 syndrome, and propose to label it “post-COVID-19 tachycardia syndrome.”

Potential distinctions and overlaps among post-acute COVID-19 syndrome, other sub-syndromes and post-acute COVID-19 syndrome, as well as postural orthostatic tachycardia syndrome, inappropriate sinus tachycardia, and sinus tachycardia in post-COVID-19 tachycardia syndrome are displayed in [Figures 1A and B](#), respectively.

Moreover, tachycardia can be considered a universal and easily obtainable quantitative marker of post-acute COVID-19 syndrome and its severity rather than patient-reported symptoms, blood testing, and thoracic computed tomography scans. Not only does it reflect autonomic dysfunction, chronic inflammation, possible myocardial injury, or neurophysiological distress, but may reveal the general status of the patient being unhealthy. Holter ECG monitoring and the plethora of mobile personal heart rhythm tracking devices may facilitate diagnosis and treatment monitoring in outpatient settings.

CLINICAL SIGNIFICANCE

- Post-acute COVID-19 syndrome is a novel clinical syndrome with symptoms beyond 4-12 weeks after a SARS-CoV-2 infection
- Tachycardia is commonly reported in these patients and may be considered a distinct phenotype
- Putative mechanism for tachycardia in this setting include dysautonomia
- Post-acute COVID-19 syndrome patients reporting palpitations should be subjected to basic cardiovascular evaluation (including head-up tilt testing if concomitant orthostatic intolerance)
- Treatment options include cardiovascular drugs and structured rehabilitation program

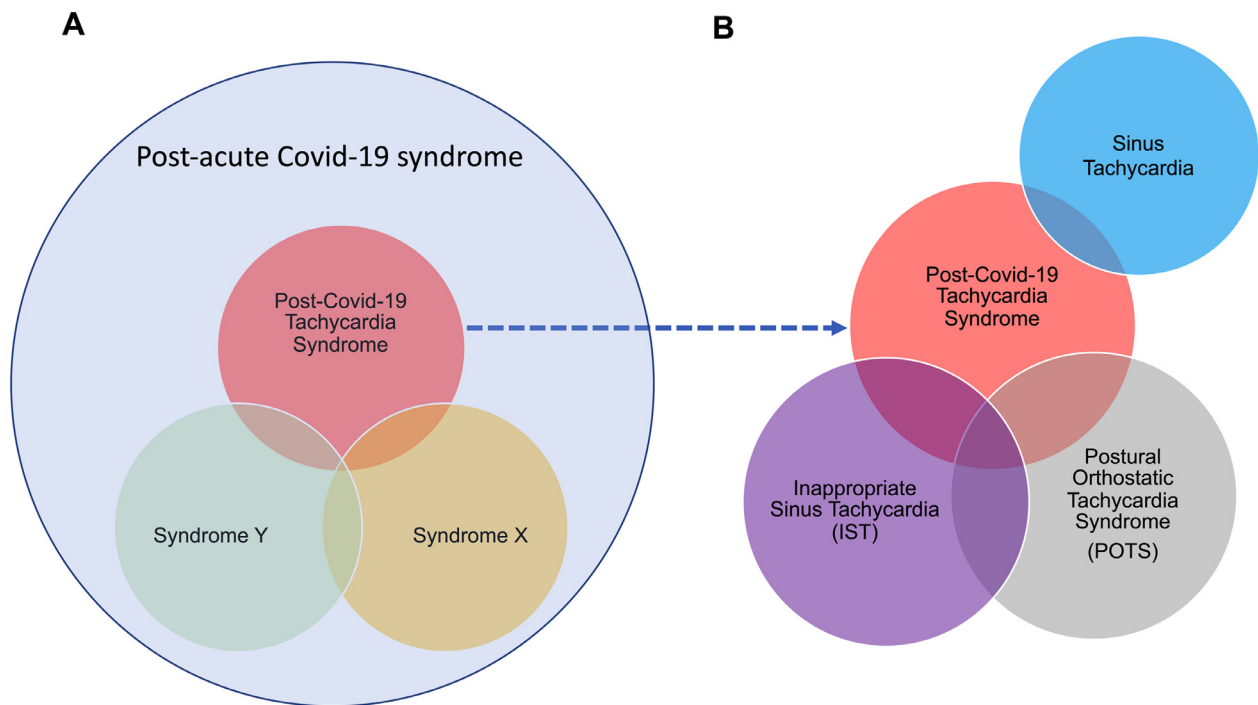


Figure 1 Potential distinctions and overlaps between post-COVID tachycardia syndrome and other sub-syndromes in post-acute COVID-19 syndrome. COVID = coronavirus disease.

PUTATIVE MECHANISMS FOR SYMPTOMATIC TACHYCARDIA IN POST-COVID-19 TACHYCARDIA SYNDROME

Postural orthostatic tachycardia syndrome is characterized by autonomic dysfunction causing a variety of symptoms, including tachycardia following postural change.⁹ It has previously been documented that viral infections can trigger postural orthostatic tachycardia syndrome.¹⁰ The pathophysiological mechanism in postural orthostatic tachycardia syndrome remains elusive but there is evidence of autoimmunity, that is, autoantibodies activating adrenergic and muscarinic receptors;¹¹ a hyper-adrenergic state;¹² peripheral denervation, similar to taste and smell loss, causing blood pooling in the lower extremities; and reflex tachycardia¹³ and deconditioning.⁹ In addition, magnetic resonance imaging studies revealed lesions in the midbrain, suggesting that central sympathetic activation may be involved as well.¹⁴ All these mechanisms may contribute to tachycardia in postural orthostatic tachycardia syndrome. Whether the same mechanisms are responsible for post-acute COVID-19 syndrome-associated postural orthostatic tachycardia syndrome and to what extent they contribute to post-COVID-19 tachycardia syndrome remain to be established.

Inappropriate sinus tachycardia is defined as an average heart rate exceeding 90 beats per minute on 24-hour ECG monitoring or a resting heart rate >100 beats per minute, and may have several causes, such as gain-of-function mutation in the cardiac pacemaker HCN4 channel,¹⁵ cardiac intrinsic sinus node abnormality, autoimmunity, excess sympathetic activation, or vagal withdrawal.⁸ Clearly,

several pathophysiological mechanisms are shared between postural orthostatic tachycardia syndrome and inappropriate sinus tachycardia, but the mechanism for inappropriate sinus tachycardia in the context of post-acute COVID-19 syndrome needs to be established.

Regarding tachycardia in post-acute COVID-19 syndrome, there may be several other factors contributing to the observed heart rate elevation. SARS-CoV-2 enters cells by attaching its spike protein to the angiotensin-converting enzyme 2 receptor, which is abundant in several different cell types and tissues, and the virus therefore can cause injury in several organs.¹⁶ Structural injury to the lungs, kidneys, pancreas, and heart have been reported in COVID-19, acutely as well as months after the occurrence of first symptoms, also in low-risk non-hospitalized patients.^{17,18} In addition, COVID-19 may damage the cardiovascular system by other mechanisms such as hyperinflammation, hypercoagulability with thrombosis, and dysfunction of the renin-angiotensin-aldosterone system.^{19,20} These factors may contribute to the observed and reported tachycardia in post-acute COVID-19 syndrome.

In addition to direct and indirect damage caused by the viral infection, there may be several other mechanisms contributing to post-COVID-19 tachycardia syndrome, for example: 1) Persistent pulmonary injury or exacerbation of underlying lung disease causing desaturation and reflex tachycardia;²¹ 2) persistent or intermittent fever, which may increase heart rate;³ 3) pain; 4) anxiety and depression;³ 5) neuroinflammation; and 6) hypovolemia. Given the novelty of the disease and the lack of basic and clinical data, several unknown mechanisms may also play a role in post-COVID-19 tachycardia syndrome.

PROPOSED CARDIOVASCULAR ASSESSMENT IN PATIENTS WITH POST-COVID-19 TACHYCARDIA SYNDROME

We suggest liberal use of at least basic cardiovascular assessment in patients with post-acute COVID-19 syndrome to identify patients with post-COVID-19 tachycardia syndrome (and associated postural orthostatic tachycardia syndrome and inappropriate sinus tachycardia). A 24-hour ambulatory ECG is recommended to detect arrhythmias, assess average heart rate, detect abnormal pulse reactions, and link symptoms to heart rate abnormalities. **Figure 2** displays 2 ECGs from patients who meet the criteria of post-acute COVID-19 syndrome. The first ECG (**Figure 2A**) shows short runs of symptomatic sinus tachycardia (marked with orange arrows) and a typical excessive increase in heart rate in the morning when shifting from bedrest to upright body position (green arrow). These are 24-hour ECG patterns raising suspicion of postural orthostatic tachycardia syndrome. The second ECG shows an elevated average sinus rate of 93 beats per minute, which is consistent with inappropriate sinus tachycardia.

Patients with Holter ECG findings suggestive of postural orthostatic tachycardia syndrome or presenting with symptoms of orthostatic intolerance should optimally perform a head-up tilt test or, at least, an active standing test to confirm the diagnosis.⁹ 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 postural orthostatic tachycardia syndrome.⁹

A transthoracic echocardiogram should be performed to exclude cardiac abnormalities.

Cardiovascular magnetic resonance (CMR) studies have reported a prevalence of myocarditis ranging from 27%-60% in patients recovering from COVID-19.^{17,22} Because perimyocarditis may cause tachycardia, we argue that CMR should be considered in the setting of typical or atypical chest pain, elevated cardiac biomarkers, or typical ECG changes. Moreover, CMR should be performed when cardiovascular autonomic testing did not lead to a diagnosis of cardiac autonomic disturbance (postural orthostatic tachycardia syndrome or inappropriate sinus tachycardia), and the patient reports abnormal or rapid heartbeats.

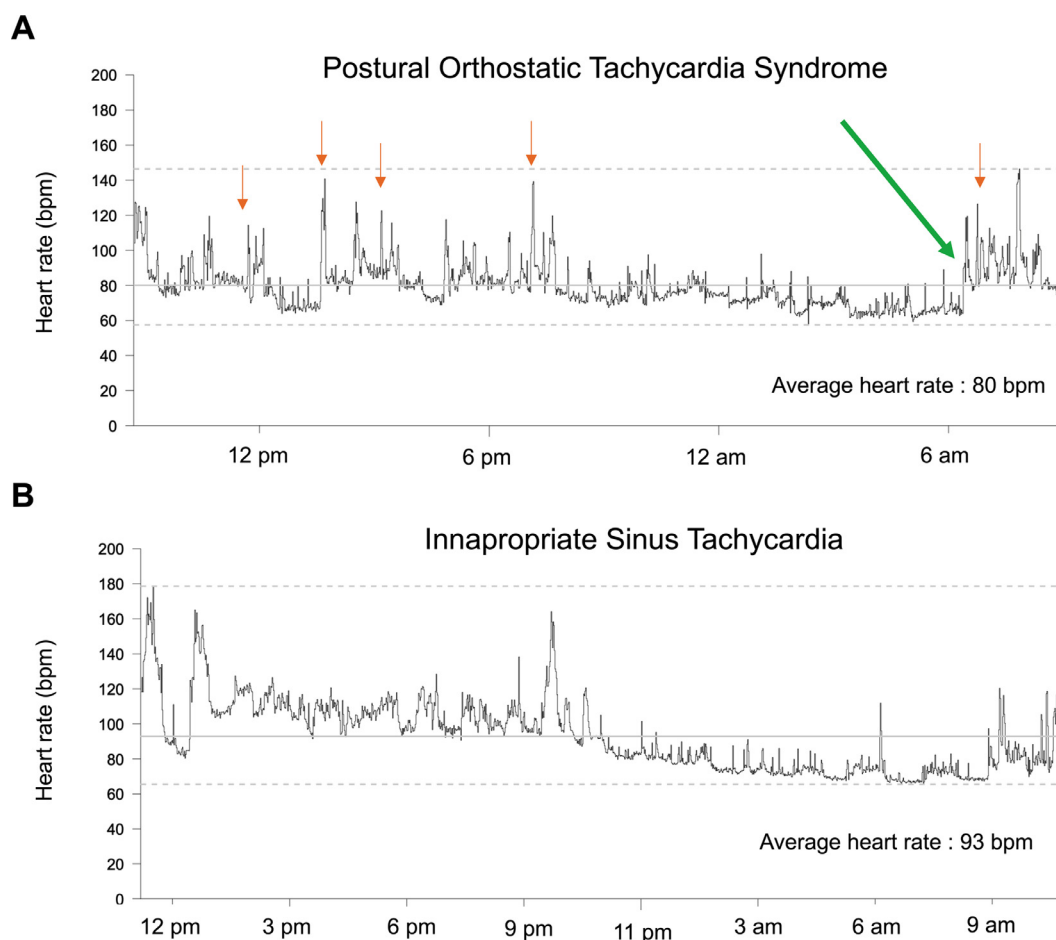


Figure 2 Examples of 24-hour Holter electrocardiogram monitoring from patients with post-COVID tachycardia syndrome due to (A) postural orthostatic tachycardia syndrome and (B) inappropriate sinus tachycardia. COVID = coronavirus disease.

Blood tests are recommended also, to evaluate extracardiac causes of tachycardia (autoimmune biomarkers, endocrine tests, inflammation biomarkers, autoimmune biomarkers, and hemoglobin levels). Pulmonary pathology is a common source of tachycardia, and basic evaluation should also include peripheral oxygen saturation (at rest and during physiological stress, such as a 6-minute walk test), thoracic computed tomography scan, and spirometry.

POSSIBLE TREATMENT FOR POST-COVID TACHYCARDIA SYNDROME

Current treatment of postural orthostatic tachycardia syndrome includes the selective sinus node inhibitor ivabradine,²³ beta-blockers,⁹ and compression garments²⁴ to stabilize cardiovascular regulation. Other pharmacological options to reduce associated symptoms are midodrine (symptoms of low blood pressure or cerebral hypoperfusion; peripheral blood pooling), pyridostigmine (muscle weakness; associated gastrointestinal dysfunction) and modafinil (brain fog).²⁵ A structured, regular, and supervised rehabilitation program is also recommended.²⁵ Immunomodulation and drugs targeting possible associated mast cell activation syndrome have not been systematically evaluated in postural orthostatic tachycardia syndrome, but might be considered *ex iuvantibus* if the typical clinical manifestation is present.²⁶

Although postural orthostatic tachycardia syndrome in the context of COVID-19 may be different from the “traditional” postural orthostatic tachycardia syndrome (pre-COVID-19), we suggest starting patients with post-acute COVID-19 syndrome and postural orthostatic tachycardia syndrome on heart rate-lowering drugs and a rehabilitation program. Other pharmacological interventions may also be considered but should be carefully monitored.

Whether patients with post-COVID-19 tachycardia syndrome are responsive to heart rate-lowering drugs and other symptomatic treatment previously used in postural orthostatic tachycardia syndrome remains to be established.

FUTURE ENDEAVORS

Basic and clinical research programs to characterize post-COVID-19 tachycardia syndrome and determine similarities and disparities with other sub-syndromes of post-acute COVID-19 syndrome are highly warranted. A clear aim should be to improve our understanding of the pathophysiology of long-term post-COVID-19 complications and to find novel targets for interventions that may provide disease-modifying effects rather than focusing on pure symptom control.

We therefore call for large registries containing both clinical data and biomarkers, and interventional studies testing the efficacy of drugs used previously in traditional postural orthostatic tachycardia syndrome, alone or in combination with experimental drugs targeting putative mechanism in post-COVID-19 tachycardia syndrome.

CONCLUSIONS

We highlight the phenomenon of abnormal sinus tachycardia in patients with post-acute COVID-19 syndrome. We propose that post-COVID-19 tachycardia syndrome should be considered a phenotype or sub-syndrome of post-acute COVID-19 syndrome. This provides a safety net for those who have multiple symptoms besides the tachycardia and who subsequently may not even mention this to their health care provider.

Post-COVID-19 tachycardia syndrome may present as postural orthostatic tachycardia syndrome or inappropriate sinus tachycardia, and likely contributes to several symptoms and the physical and mental disabilities in post-acute COVID-19 syndrome. Future studies should focus on biological and clinical characterization of this novel clinical syndrome and interventional studies, testing established and novel pharmacological approaches.

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