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Review Article

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Comprehensive overview of Postural Tachycardia Syndrome (POTS) in patients with SARS-COV-2 virus, prevalence, causes and treatment

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ABSTRACT

The disease of Covid-19 (Covid-19), which is caused by the SARS-CoV-2 virus, can include symptoms or abnormal clinical parameters and medical consequences that last from two or more weeks to months after the initial recovery, which is the so-called Long- COVID or long-term Covid. Although such a change is most often reported in survivors of severe and critical illness, lasting effects also occur in people with mild infections who do not require hospitalization. Postural tachycardia syndrome (POTS), a persistent tachycardia with a persistent increase in heart rate without marked hypotension, has been increasingly reported in patients with SARS-CoV-2. In this study, symptoms, prevalence rate, mechanisms of occurrence and treatment management of the disease have been investigated with a review approach on published studies.

Keywords: *Covid-19, SARS-CoV-2 virus, Long-term Covid, POTS*

The prevalence of Postural Orthostatic Tachycardia Syndrome (POTS) following COVID-19 infection

Since the onset of the COVID-19 pandemic, there have been increasing reports of patients with chronic symptoms, known as long-term COVID [1-3]. At the beginning of the COVID-19 epidemic, in a group of patients with COVID-19, heart palpitations were observed in 7.3% of patients [4, 5]. A preliminary study on hospitalized patients with COVID-19 in Wuhan Hospital also found the occurrence of cardiac arrhythmia in 17% of patients, which reached 44% in patients hospitalized in the ICU. Dysautonomia is a post-acute neurological complication that explains the persistent symptoms observed in long-term covid [6]. Postural Tachycardia Syndrome (POTS) is the most common dysautonomia characterized by sustained tachycardia with a persistently elevated heart rate (30 beats per minute or more) in the absence of orthostatic hypotension and is increasingly common in patients with

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reported to SARS-CoV-2 [7]. Therefore, it can be said that POTS is a circulatory disorder that affects the autonomic nervous system [8]. Acute stressors, including immunostimulants such as frequent viral infections of the upper respiratory tract or digestive tract, vaccination, pregnancy, surgery, and traumatic events, trigger POTS [9-12]. Among them, viral infections are the most commonly reported cause of POTS disorder (28-41% of POTS patients) [10]. The most common symptoms of this disorder include fatigue, nausea, dizziness, lightheadedness, heart palpitations, chest pain, and exercise intolerance [12]. In general, there is no accurate report of the prevalence of POTS worldwide. However, based on US estimates, an estimate of 0.1 to 1% for the prevalence of this disease has been reported. However, women are affected by this disorder more than men with a ratio of 4:1 [13, 14]. According to a 2022 study, 26 people with POTS disorder and severe symptoms that appeared several weeks after infection with the SARS-COV-2 virus and lasted for more than months were reported. Among them, the age of these people was between 22-59 years, and women had a greater share (69%) [13]. In another study by Blitshteyn. S et al., it was observed that among the 20 patients studied with COVID-19, 70% of whom were women, 15 of them had POTS disorder, 3 had neurocardiogenic syncope, and 2 had hypertension. They were low orthostatic (orthostatic hypotension) [15]. There have been reports of POTS disorder in COVID-19 patients in Iran. For example, Eslami. M et al studied 60 patients with COVID-19 disease who were admitted to Imam Khomeini Hospital (RA) in Tehran. The average age of the patients was 56.6 years and 42 of them were men. The results of examining these people two months after contracting the COVID-19 disease showed that the most common cardiovascular risk factor is high blood pressure (35%). Also, 29 patients (48.3%) had POTS disorder [16]. Therefore, these reports are an alarm that shows that POTS as a post-coronavirus disorder is increasing in the world and in Iran.

Occurrence mechanisms of postural orthostatic tachycardia syndrome (POTS)

Although there are several mechanisms in the occurrence of POTS, the three main mechanisms of this disorder include hypovolemia, neurotropin, inflammation, and autoimmunity [17, 18].

Hypovolemia

It has been proposed that POTS occurs due to reduced blood volume and loss of cardiac conditioning, which subsequently increases the cardiac sympathetic nervous system (SNS) [19, 20]. COVID-19 can be associated with fever and night sweats, leading to hypovolemia. On the other hand, long-term bed rest, in the condition of convalescence of this disease, leads to cardiac atrophy [11]. In addition, it has been reported that people with POTS have a lower plasma volume than healthy people. Therefore, it can be concluded that the renin-angiotensin-aldosterone system (RAAS) plays a role in reducing the plasma volume of these people. In this regard, SARS-CoV-2 also plays a role in binding and reducing the expression of ACE2 receptor and causing RAAS imbalance [11, 21, 22]. It has also been suggested that SARS-CoV-2 causes cellular furin deficiency, resulting in impaired epithelial sodium channel (ENaC) function and changes in fluid balance that activate the RAAS[23].

Neurotropsin

The most important cause of POTS is the destruction of SARS-CoV-2 in the cells of the central nervous system (CNS) [18]. Getting infected with the disease of COVID-19 can directly cause damage to these cells by causing inflammation in nerve cells [24]. ACE2 receptors, through which SARS-CoV-2 enters the host cell, are highly expressed in the olfactory epithelium. Therefore, a proposed route of transmission of SARS-CoV-2 through the nose is through the cribriform plate of the ethmoid bone to the olfactory epithelium, which could be responsible for the hyposmia observed with infection with this virus [25]. Thus, SARS-Cov2 could infect the extracardiac postganglionic SNS and lead to dysautonomia in a manner similar to neuropathic POTS. This disorder can lead to tachycardia caused by splanchnic venous accumulation or reduced contraction of mesenteric vessels during orthostasis [17].

Inflammation and autoimmunity

The role of the autoimmune system and inflammation in the etiology of POTS appears with the increase of antibodies and the occurrence of autoimmune conditions seen in patients with POTS compared to the control group [26]. COVID-19 infection can cause severe release of cytokines, inflammation, and chronic neurological disorder [27]. This is through the creation of autoantibodies that cross-react with the autonomic

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ganglia as part of the acute and long-term infection of COVID-19, leading to dysautonomia and POTS [28, 29]. It should be noted that there are reports about the effect of anti-coronavirus vaccines on the development of POTS [30, 31]. For example, Hermel. M et al reported that a 46-year-old woman experienced 3 episodes of POTS after receiving the Pfizer anti-coronavirus vaccine [31]. A German group also reported their observations of 5 patients aged 37, 21, 46, 19 and 17 years after receiving Moderna and Pfizer anti-coronavirus vaccines to their clinic [32]. One of the reasons for this can be the free floating spike proteins that are synthesized as the target cells of vaccines and systematically interact with ACE2 receptors in the circulating blood, which causes the accumulation of pockets, the formation of clots and inflammation.[33, 34].

Management and treatment of postural tachycardia syndrome

Primarily, when a patient with suspected POTS presents with symptoms such as gastrointestinal or urinary dysfunction, abnormal sweating, acrocyanosis, dry mouth, and unexplained fever and headache, physicians should perform a physical examination including orthostatic vital signs at regular intervals. Check 12-lead electrocardiography from standing (recording related symptoms). Also, the 24-hour Holter monitor can detect the presence of inappropriate sinus tachycardia [35]. Laboratory investigations such as hemoglobin, electrolytes, kidney function, ferritin, thyroid-stimulating hormone and morning cortisol should also be performed as secondary causes of orthostatic tachycardia [36]. Using drug treatments for this disorder is usually not the first solution, but their goal is to correct several physiological components [37, 38]. However, drugs such as fludrocortisone, erythropoietin, and desmopressin to increase blood volume, β-blockers such as propranolol and ivabradine which act like β-blockers, to reduce tachycardia, midodrine, methylphenidate and octreotide to induce vasoconstriction, and pyridostigmine to facilitate synaptic transmission are used. (Table 1) [11, 37, 39]. However, currently, conservative treatment options including graded exercise programmes, avoidance of stimulants, fluids and high salt in hyperadrenergic POTS, and use of compression stockings and cognitive-behavioral therapy are suggested for the management and treatment of postural tachycardia syndrome. [37]. Therefore, it is clear that more research is needed to investigate the underlying mechanisms of dysautonomia and targeted treatment options.

Table 1: Proposed Medications for the Treatment and/or Improvement of Symptoms of POTS.

Drug Class	Drug	Dosage	Effectiveness	Side Effects
Heart rate reducers	Propranolol	10-20 mg maximum, twice-four times a day	Medium	Reducing blood pressure, bradycardia and bronchospasm
	Ivabradine	5-7.5 mg, twice a day	Medium	Visual disorders and bradycardia
	Pyridostigmine	30-60 mg, three times a day	Low	Increased stomach movements, diarrhea, abdominal cramping
vasoconstrictors	Midodrine	2.5-10 mg, three times a day	Medium	Tingling scalp and high blood pressure
Sympatholytics	Methyldopa	125-250 mg, three times a day	Low	Lower blood pressure, weakness and brain fog , headache, constipation
	Clonidine	0.05-0.2 mg, twice a day	Low	Mental clouding, fatigue, constipation, dry mouth
Blood volume enhancers	Fludrocortisone	0.05-0.1 mg per day	Low	Hypokalemia* and hypertension, edema, headache
	Desmopressin	0.1-0.2 mg per day -twice a day	Low	Hyponatremia *,headache, hypertension

*Hypokalemia: Low blood potassium levels ,*Hyponatremia: Blood sodium is lower than normal

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