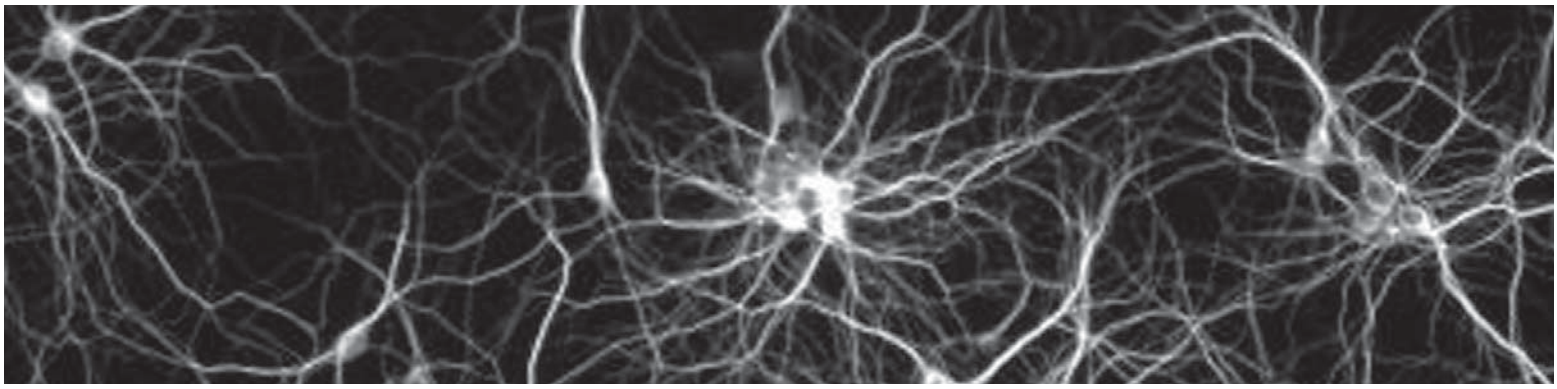

Postural orthostatic tachycardia syndrome

L. Crnošija[1], I. Adamec[2], A. Mišmaš[2], M. Habek[1,2]

ABSTRACT - Orthostatic intolerance can be defined as inability to tolerate upright posture relieved by recumbence. Postural orthostatic tachycardia syndrome (POTS) is a form of orthostatic intolerance defined as sustained increase in heart rate of ≥30 bpm or increase of heart rate to ≥120 bpm within 10 min of standing or head-up tilt associated with symptoms of orthostatic intolerance and absence of orthostatic hypotension. POTS patients are mostly female with 4-5:1 ratio and age range from 15 to 50. Several pathophysiological mechanisms are thought to underlie POTS. Some of the possible mechanisms are distal peripheral neuropathy, abnormalities of central control of sympathetic nervous system, impaired synaptic norepinephrine reuptake, renin-angiotensin-aldosterone axis disturbance and altered norepinephrine synthetic pathway. The most common symptoms related to POTS are light-headedness, presyncope, weakness and palpitations. Exacerbation of symptoms with standing and symptoms relieved with recumbence is a characteristic feature of POTS. Active stand test and passive head-up tilt table test are used in diagnosing POTS, along with detailed history and examination. Nonpharmacological therapy of POTS includes increase in daily salt and water intake, and exercise training. Pharmacological therapy is directed at expanding fluid volume, increasing peripheral vascular resistance and reducing central sympathetic activity. The majority of patients experience substantial improvement after correct diagnosis and appropriate therapy.

Key words: orthostatic intolerance, postural orthostatic tachycardia syndrome (POTS), pathophysiology, neuropathic POTS, hyperadrenergic POTS, diagnosis, therapy

INTRODUCTION

Orthostatic intolerance (OI) can be defined as inability to tolerate upright posture relieved by recumbence. Patients with OI experience characteristic symptoms and signs during orthostasis. These include loss of consciousness, visual difficulties, lightheadedness-dizziness, headache, fatigue, orthostatic hypotension and sometimes hypertension, weakness, nausea and abdominal pain, sweating, tremulousness (1). Depending on the level of sympathetic activity, patients with OI can be classi-

[1]School of Medicine, University of Zagreb, Zagreb, Croatia

[2]Zagreb University Hospital Center, Department of Neurology, Referral Center for Demyelinating Diseases of the Central Nervous System, Zagreb, Croatia

fied into two types. One type comprises patients with diminished sympathetic activity who develop hypotension during standing. This is acute in those with vasovagal syncope and chronic in patients with central or peripheral neurodegenerative diseases. The second type patients have increased sympathetic activity, without development of hypotension and with notable tachycardia as a response to orthostasis. The latter is referred to as postural orthostatic tachycardia syndrome (2).

The postural orthostatic tachycardia syndrome (POTS) is a form of orthostatic intolerance defined as a sustained heart rate (HR) increment of ≥30 bpm (3-5), or increase of heart rate to ≥120 bpm within 10 min of standing or head-up tilt associated with symptoms of orthostatic intolerance and absence of orthostatic hypotension. For individuals aged 12-19 years, the required increment is at least 40 bpm (3). Diehl proposes a surrogate criterion for diagnosing POTS in patients with typical symptoms but not fulfilling the HR increment of ≥30 bpm or HR ≥120 criterion as HR increase between minutes 5 and 10 of more than 8 bpm during head-up tilt test (6).

The aim of this review is to investigate and summarize the latest literature on POTS.

EPIDEMIOLOGY

POTS patients are mostly female with 4-5:1 ratio and age range from 15 to 50 (4), but with relatively few patients over the age of 40 (7). This demographics may be due to the effect of female sex hormones on adrenergic receptor sensitivity and norepinephrine (NE) metabolism (8,9). The true prevalence is not known, but is likely to be higher than 170 cases *per* 100,000 (10).

PATHOPHYSIOLOGY

Normal physiology of standing

Within a few seconds of assuming upright from previously supine position, 300-800 mL of blood is gravitated downwards from the thorax into the abdomen and lower limbs, thus decreasing venous return to the right side of the heart causing reduction in stroke volume and cardiac output. These changes are then registered by arterial baroreceptors and cardiopulmonary mechanoreceptors leading to activation of compensatory reflexes – increased sympathetic and reduced parasympathetic nervous system output with final outcomes of peripheral arterial vasoconstriction and reduced vagal tone to the heart with cardio-acceleration (4). Normal subjects react with 5 to 15 bpm increase in heart rate, systolic blood pressure remains stable and diastolic blood pressure rises slightly (about 5-10 mm Hg) (4,6). It is important to note that this reaction is swift and occurs within the first minute of assuming the upright position in normal subjects (6).

Several underlying mechanisms are thought to be involved in the pathophysiology of POTS.

Neuropathic

Some studies link POTS with partial dysautonomia, which predominantly affects lower limbs. Evidence supporting this hypothesis will be mentioned hereafter. Jacob *et al*. examined sympathetic nervous system function by measuring norepinephrine-spillover in response to three stimuli: cold pressor test, nitroprusside and tyramine infusion (11). These stimuli increased norepinephrine-spillover to similar extent in arms of normal subjects and POTS patients, but failed to increase it in the legs of POTS patients. One study showed that arterial vasoconstriction, which is normal response to orthostasis, is impaired in POTS patients (12). This finding is consistent with defective norepinephrine secretion (11,12). In an animal model of neuropathic POTS, partial dysautonomia in rats was achieved by selectively lesioning peripheral postganglionic sympathetic neurons using neurotoxin 6-hydroxydopamine hydrobromide (6-OHDA) resulting in significant heart rate increase (13). Vascular α1-sensitivity examined with selective agonist phenylephrine was also increased after administration of 6-OHDA. The latter finding is consistent with the early work of Streeten in which he describes hypersensitivity of foot veins to NE infusion typical of denervation (14). Distal sudomotor abnormalities can be found in approximately half of patients with POTS (7,15), although this finding does not appear to correlate with symptom measurements (15).

Taking these findings into account, it can be concluded that the neuropathic form of POTS is caused by distal peripheral neuropathy resulting in inadequate vascular response to orthostatic stress. This leads to excessive venous blood pooling and increased capillary filtration in lower extremities causing functional decline in circulatory volume, which results in a compensatory increase in HR and myocardial contractility (6). It has been esti-

mated that neuropathic POTS is the most common form of POTS (16,17).

Hyperadrenergic

The hyperadrenergic form of POTS is less frequent, accounting for about 10% of POTS patients. Patients with this form of POTS often display orthostatic hypertension, significantly elevated serum norepinephrine (>600 pg/mL or >3.5 nmol/L) on standing or exaggerated response to intravenous isoproterenol. This group of patients appear to have abnormalities of central control of sympathetic nervous system or defective norepinephrine uptake resulting in excess systemic NE spillover (4,16-18). Some studies reported abnormally low concentration of plasma dihydroxyphenylglycol (DHPG), intraneural NE metabolite, in relation to NE concentration, providing evidence of impaired NE uptake (19-21). In some patients, hyperadrenergic response may be a compensatory reaction to hypovolemia or peripheral neuropathy with venous pooling (4).

Genetic

Norepinephrine transporter (NET) is a presynaptic transporter responsible for the clearance of approximately 70% of synaptic NE (19). Heart is more sensitive to impairments in NE reuptake because cardiac sympathetic nerves recapture at least 80% of released NE (22). Point mutation of gene encoding NET resulting in 98% loss of function has been recorded in one POTS patient (21). Two studies showed reduced NET protein expression in POTS patients (20,22). In the work by Schroeder *et al*., POTS-like phenotype was achieved in healthy subjects by administering 8 mg of reboxetine, a selective NET blocker (23). Impaired NE clearance in the synaptic cleft may result in excess NE spillover and consequent elevated NE plasma levels. The relation between impairment of NE reuptake and POTS symptoms is unknown (20,22), except for tachycardia, which might be explained by failure of clearance of NE from cardiac sympathetic nerve synaptic spaces (22).

Renin-angiotensin-aldosterone system and blood volume perturbation

The renin-angiotensin-aldosterone system (RAAS) plays a vital role in blood volume control. In response to hypovolemia, juxtaglomerular cells secrete renin, which then enzymatically acts on its substrate, angiotensinogen, and produces angiotensin I (Ang I). Ang I is then converted to angiotensin II (Ang II) *via* systemic or locally produced angiotensin-converting enzyme (ACE). Ang II promotes sodium and water retention, both directly by stimulating sodium reabsorption in the proximal tubule and indirectly by stimulating aldosterone secretion. Mineralocorticoid aldosterone regulates sodium transport at several sites in the kidney, thus controlling water retention with the effect on plasma volume (24-26). Ang II is further degraded to Ang-(1-7) by angiotensin converting enzyme (ACE2). ACE2 also converts Ang I to Ang-(1-9), which is thereafter converted to Ang-(1-7). Binding of Ang-(1-7) to Ang-(1-7) receptors induces vasodilatation (27). Ang II has various other effects besides those already mentioned. Ang II is involved in a control loop as negative feedback to renin production (26). Ang II can increase central sympathetic outflow by binding to AT-1 receptors (angiotensin II Type I receptor) in the circumventricular organs of the brain (25). It can also increase the release of NE from ganglionic and postganglionic sympathetic nerves (25,26), and inhibit NE reuptake in the nerve terminals with consequential effect on vasoconstriction (26). It also has direct vasoconstrictive action by binding to AT-1 receptors on smooth muscle cells. Ang II has been shown to decrease bioavailable nitric oxide (NO) (26). Essentially, Ang II is a potent vasoconstrictor and important regulator of plasma volume.

Some POTS patients exhibit low blood volume and inappropriately low plasma renin activity (PRA) and aldosterone concentration (22,24-26), a state sometimes referred to as 'renin-aldosterone paradox' (24). In the work by Raj *et al*., patients with POTS had a mean plasma volume deficit of almost 350 mL (24). At least two studies have reported positive correlation between PRA and blood volume in POTS patients with low blood volume, when negative correlation would be expected (26,29). Several studies have reported POTS patients with increased level of plasma Ang II (25,26,28). Mustafa *et al*. report on blunted systemic vasopressor, but not renal vascular or adrenal secretionary response to Ang II infusion in patients with POTS (28). This study also reports on POTS patients to have blunted baseline spontaneous baroreflex sensitivity (BRS), which showed significant negative correlation to baseline levels of plasma Ang II. Mustafa *et al*. hypothesize that high levels of Ang II could be explained by decreased ACE2 activity (28). This hypothesis is reinforced with findings of another study in which targeted disruption of ACE2 in mice resulted in increased

Ang II levels (30). The work by Stewart *et al*. provides evidence for the latter hypothesis, but they also hypothesize that defective ACE2 resulting in decreased levels of Ang-(1-7) might contribute to excessive vasoconstriction found in some POTS patients (26,27). This subgroup of POTS patients are referred to as low-flow POTS patients (27).

These data suggest that defects in RAAS may play an important role in the pathophysiology of POTS, particularly in a subset of POTS patients with low blood volume and increased level of Ang II.

Altered norepinephrine synthetic pathway

NE is synthesized *via* tyrosine hydroxylation to dihydroxyphenylalanine (DOPA), DOPA decarboxylation to dopamine (DA). DA is then converted to NE through dopamine beta hydroxylase (DBH) action. Garland *et al*. measured DOPA and DA in POTS patients for the first time and found a significantly increased level of DA, along with reduction in supine DOPA (19). The authors hypothesize that a higher NE/DOPA ratio in combination with a higher plasma DA may be consistent with activation of either DOPA decarboxylase or DBH in POTS patients. This could explain high plasma NE in some POTS patients.

The "Grinch syndrome"

In the study by Fu *et al*., 27 POTS patients were submitted to autonomic function test, cardiac magnetic resonance imaging (MRI), and 19 patients completed 3-month exercise training program (31). The following results were obtained: blood and plasma volume were markedly reduced in patients, left ventricular mass in POTS patients was much smaller compared to healthy sedentary controls, patients had smaller cardiac output and stroke volume in both supine and upright postures, as well as greater peripheral resistance than controls. In 19 patients who completed 3-month training program, the peak oxygen uptake, blood volume and plasma volume increased significantly. Ten out of 19 patients no longer met POTS criteria after training. Orthostatic tachycardia observed in these patients appeared to be a physiological compensatory response to the smaller stroke volume, which was attributable to cardiac atrophy and reduced blood volume. These results suggest that POTS may be a consequence of "deconditioning" (i.e. cardiac atrophy and hypovolemia), and that carefully prescribed exercise training can be used as a non-drug treatment for patients with POTS. The authors propose a new term for POTS, the "Grinch syndrome" after the main character in Dr. Seuss's book *How the Grinch Stole Christmas*, who had a heart that was "two sizes too small", emphasizing that a small heart is the primary abnormality and target for therapy.

It is likely that the pathophysiological mechanisms mentioned here are intertwined and that POTS is a result of their combination.

CLINICAL MANIFESTATIONS

About half of patients with the neuropathic form of POTS experience acute or subacute onset of symptoms, often preceded by viral illness. It is presently felt that neuropathic POTS is of autoimmune nature in many cases, which is supported by the presence of acetylcholine receptor ganglionic (G-AchR) antibodies in 15%-25% of POTS patients (7,16,32). Some patients report that their symptoms begin after pregnancy, surgery, sepsis or trauma (10, 16,17). On the other hand, patients with the hyperadrenergic form of POTS often describe a more gradual and progressive appearance of symptoms over time rather than abrupt onset (17,21). One case report attributes the onset of reversible POTS to inadvertent overuse of Red Bull® (33). POTS may be secondary to a variety of conditions that produce a state of peripheral autonomic deinnervation or vascular unresponsiveness with relative sparing of cardiac innervation. A frequent cause of secondary POTS is chronic diabetes mellitus. Other possible causes are amyloidosis, sarcoidosis, alcoholism, lupus, Sjögren syndrome, chemotherapy and heavy metal poisoning. POTS can be a form of paraneoplastic syndrome that can be seen with adenocarcinomas of the lung, breast, ovary and pancreas (17).

Symptoms associated with POTS are numerous. Thieben *et al*. performed a retrospective study involving 152 POTS patients (7). Clinical features documented in this study will be listed hereafter. Symptoms presumably related to cerebral hypoperfusion: light-headedness, 77.6%, presyncope, 60.5%, and weakness, 50.0%. Symptoms presumed to be associated with autonomic overactivity: palpitations, 75.0%; tremulousness, 37.5%; shortness of breath, 27.6%; and chest wall pain, 24.3%. Sudomotor symptoms: loss of sweating, 5.3%; and hyperhidrosis, 9.2%. Several of the chronic symptoms reported may reflect dysautonomia: gastrointestinal complaints, including bloating, 23.7%; nausea, 38.8%; vomiting, 8.6%; abdominal pain, 15.1%;

constipation, 15.1%; diarrhea, 17.8%; bladder dysfunction, 9.2%; and pupillary dysfunction, 3.3%. Generalized complaints: 48.0% experienced fatigue, 31.6% experienced pronounced sleep disturbance, 27.6% had migraine headache, and 15.8% had myofascial pain. Kanjawal *et al*. retrospectively analyzed 27 patients with hyperadrenergic POTS, with the following results: 55%-65% of patients reported symptoms of hyperadrenergic state in the form of anxiety, tremulousness and excessive sweating; orthostatic palpitation was reported by 13 (48.2%) and syncope by 11 (40.7%) patients (16). About 30% of POTS patients have neurally mediated syncope (34).

Symptoms get worse with standing and are relieved with recumbence (34). Aggravating factors include heat or exercise (53.3%), postprandial symptoms (23.7%), and worsening at time of menses (14.5%) (7). The intensity of symptoms is variable. Some patients are severely affected and are unable to work, attend school or participate in recreational activities resulting in substantial morbidity (31).

The principal clinical sign of POTS is abnormal tachycardia on assumption of upright posture. The second frequent sign is acrocyanosis, which can extend from the feet to above the level of knees, with the occurrence of 40%-50% during standing (34). Other signs are rare and include pupillary dysfunction and symptoms consistent with peripheral neuropathy (4).

ASSOCIATED AND OVERLAPPING CONDITIONS

Chronic fatigue syndrome/myalgic encephalomyelitis

Overlapping between clinical manifestations of POTS and chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis, has been documented in the literature (7,11,35,36). The prevalence of POTS in CFS patients has ranged from 19% to 70%, while studies in cohorts of patients selected for POTS have shown a prevalence of chronic fatigue to range between 48% and 77%, and of CFS between 17% and 23% (11,35,36). In the work by Okamoto *et al*., out of 47 POTS patients enrolled in the study, 30 (64%) fulfilled the criteria for CFS (36). This study also compared groups of POTS patients with and without CFS and found that most common symptoms were unrefreshing sleep, impaired memory or concentration, and muscle pain (36).

Multiple sclerosis

Multiple sclerosis (MS) and POTS share some similar features. Typical age group is between 20 and 50 years, and women are more often affected in both conditions. Common symptoms include orthostatic intolerance, fatigue and anxiety (37). In one prospective study, out of 112 patients diagnosed with relapsing remitting MS, 21 (18.8%) of them met the criteria for POTS; 17 of those patients were in relapse (38). Another study conducted on a large sample of patients, divided into a group of 112 MS patients and a group of 181 patients with symptoms of OI, showed that POTS was more frequent in MS patients in comparison with patients with symptoms of OI with no neurologic illnesses (37). Connection between MS and POTS is explained by the presence of demyelinating brainstem and hemispheral lesions, which disrupt the physiological heart rate variability modulation (39).

Inappropriate sinus tachycardia

Inappropriate sinus tachycardia (IST) is a form of arrhythmia, which is characterized by an exaggerated increase in heart rate that is disproportionate to normal physiologic demands. IST shares some similarities with POTS. Patients with IST are also more often women, presenting symptoms are palpitations, fatigue, exercise intolerance and dizziness (4). IST can be triggered by orthostasis and minimal exertion (40), and exaggerated response to isoproterenol infusion can also be seen in IST (17). Although sometimes it can be challenging to differentiate between POTS and IST, there are some distinguishing features that can help make the correct diagnosis. POTS patients tend to display a more pronounced degree of postural change in HR than those with IST, and supine HR in POTS patients rarely exceeds 100 bpm, which is a common finding in patients with IST (4,17).

Other

Migraine is found in about 42% of POTS patients (7). Joint hypermobility, irritable bowel syndrome, inflammatory bowel disease, mitral valve prolapse, and hypertension are frequently mentioned as comorbidities associated with POTS (4,16,18,34). POTS patients are sometimes diagnosed with anxiety disorders, but that might be due to misinterpretation of their physical symptoms. Patients with POTS often have diminished attention and concentration (34).

DIAGNOSTIC EVALUATION

First, comprehensive history should be obtained and detailed examination should be performed with focus on previously described signs and symptoms. As mentioned before, a cardinal criterion in diagnosing POTS is HR increase of ≥30 bpm or increase of heart rate to ≥120 bpm within 10 min of standing or head-up tilt associated with symptoms of OI and absence of orthostatic hypotension. Two tests can be used to assess patient reaction to postural change. Passive head-up tilt table (HUT) test (Fig. 1) is the standard method, which consists of two phases. In the first phase, the patient is placed on a tilt table for 5-20 min and then supine HR and blood pressure (BP) are monitored. In the second phase, the patient is tilted to 60°-80° and HR and BP are measured periodically or continuously for 10-60 min (4,5,18,39,41). The test should be performed in a quiet, dimly lit, temperature-controlled environment (4). The time spent in supine or tilted

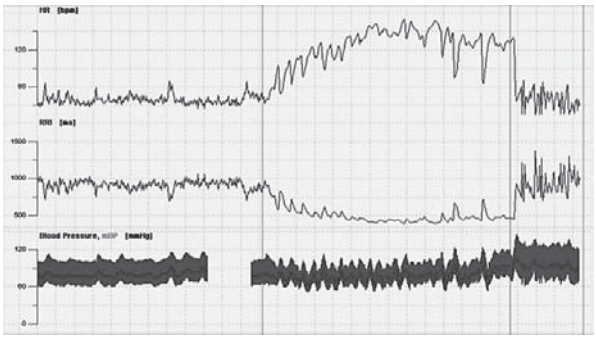

Fig. 1. *An example of head-up tilt test in a patient with POTS: upper line shows continuous heart rate monitoring, lower line shows continuous blood pressure monitoring. Note the increase of heart rate after the tilt (first vertical red line) >30 beats/minute, without fall in blood pressure.*

position depends on the protocol used. Another test is active stand test, which is considered to mimic real life. The patient is asked to assume upright position following the time spent in supine position. Whilst the patient is standing unassisted, HR and BP are measured periodically (4,5,34,41). Plash *et al*. (41) compared HUT to standing test in diagnosing POTS. In this study, 10-min standing was the most accurate test, when using the ≥30 bpm HR increment criterion. Results obtained in this study suggest that 10-min tilt test is highly sensitive (93%), but has poor specificity (40%), when using the ≥30 bpm HR increment criterion. Plash *et al*. suggest that by increasing the HR criterion to 37 bpm the test becomes much more specific (73%), while maintaining good sensitivity (80%). POTS is not diagnosed based solely on hemodynamic criteria. Clinical diagnosis of POTS requires history of orthostatic symptoms lasting for ≥6 months, worsening of symptoms with standing and relief with recumbence, absence of other causes of orthostatic symptoms or tachycardia (e.g., active bleeding, acute dehydration, medications) in addition to hemodynamic criteria. To differentiate the hyperadrenergic from neuropathic type of POTS, supine and standing serum NE levels should be obtained. A high standing NE (>600 pg/mL or or >3.5 nmol/L) identifies patients with hyperadrenergic POTS and predicts their response to β-blockade (7,17).

MANAGEMENT

It is important to educate the patient about the nature of her/his disorder. Aggravating factors, such as heat or dehydration, should be avoided. Consumption of alcohol should be discouraged (18). Patients should be taught three simple measures beneficial in improving OI. The first measure are physical countermaneuvers. Patients contract muscles below the waist for about 30 seconds, which results in reduced venous capacity and increased peripheral resistance. The second measure, which is especially helpful in patients who are hypovolemic, is wearing an abdominal binder. This reduces splanchnic-mesenteric venous capacity. The third measure is water bolus therapy, which consists of drinking two 8-ounce (≈2 dL) glasses of water consecutively inducing sympathetically-mediated pressor response (42,43).

Nonpharmacotherapy

Every POTS patient should be encouraged to begin a gradual program of physical reconditioning, with a goal of performing 20 to 30 min of aerobic activity 3 times a week (4,17). In one study, 10 of 19 POTS patients that completed 3-month exercise training program no longer met the criteria for POTS (31). This and one other study recorded increase in blood and plasma volume in patients who finished 3-month training program (44). Winker *et al*. demonstrated that training can result in shift from sympathetic to vagal predominance, which might be beneficial for patients with OI (44). Many patients with POTS are hypovolemic. These patients should increase salt intake to up to 10-20 g *per* day and take 2-2.5 L of fluids *per* day (4,34,42).

Acute blood volume expansion by applying 1 liter of physiological saline intravenously is highly effective in controlling HR and acutely improving POTS symptoms, but the treatment is not practical on a day to day basis (4,34).

Pharmacological

When nonpharmacological measures alone do not prove efficient, drugs are needed (10). The main goal of medications should be stabilization of the condition enough to enable POTS patients to undergo exercise training program (17). Patients with the neuropathic type of POTS are best treated with a combination of fludrocortisone and α-agonist midodrine (42). Daily dose of fludrocortisone should not exceed 300 μg to avoid adverse effects. Initial dose of midodrine should be 2.5 mg, three times a day before meals and can be increased if needed to a maximum recommended daily dose of 30 mg (10). Some patients have better response when midodrine is combined with the acetycholinesterase inhibitor pyridostigmine, at a dose of 60 mg 3 t.i.d. (42). Pyridostigmine appears to be most effective in patients with postviral onset of POTS (17). In patients who are unresponsive to abovementioned therapy, selective serotonine reuptake inhibitor (SSRI) or norepinephrine reuptake inhibitor can be added. Octreotide administered by subcutaneous injection beginning at 50 μg 2-3 times daily is an additional therapy for refractory patients (17). Octreotide can be beneficial in patients with marked postprandial symptoms (10). Patients with hyperadrenergic form of POTS often respond best to agents that block norepinephrine or its effects (17). Dual-acting β-blocker, such as carvedilol or labetalol, may be more effective than a pure β-blocker (e.g., propranolol). Recommended dosage for carvedilol and labetalol is 3.125-6.25 mg p.o. twice daily and 100-200 mg p.o. twice daily, respectively (18). Central sympatholytic medications, such as clonidine, are often used in patients with hyperadrenergic POTS. Clonidine, an alpha 2 agonist, is administered orally or in the patch form 0.1-0.3 mg twice daily (10,17,34). Ivabradine, a sinus node blocker, is beneficial in some POTS patients. According to one retrospective case series, ivabradine appears to control symptoms associated with POTS with effectiveness similar to that of conventional treatment (45).

According to Thieben *et al*., most commonly prescribed medications are β-blockers (76.7%), followed by SSRI (51.7%), fludrocortisone (39.5%) and midodrine (31.6%) (7).

PROGNOSIS

Younger patients and those with postviral onset of POTS have better prognosis. Over one-half of those with postviral onset make reasonable recovery over 2-5 years and are able to perform activities of everyday life with minimal restriction. Approximately 90% of patients will respond to a combination of physical and pharmacological therapy, but patients with hyperadrenergic POTS will likely require therapy indefinitely. The majority of patients experience substantial improvement after correct diagnosis and appropriate therapy (17,46,47).

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Address for correspondence: Mario Habek, MD, PhD, Department of Neurology, Zagreb University Hospital Center, Kišpatićeva 12, HR-10000 Zagreb, Croatia; e-mail: mhabek@mef.hr