

# Sindrom posturalne ostostatske tahikardije

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Crnošija, Luka

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SVEUČILIŠTE U ZAGREBU

MEDICINSKI FAKULTET

**Luka Crnošija**

**Sindrom posturalne ortostatske tahikardije**

**Diplomski rad**



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## **Kratice**

6-OHDA - 6-hydroxydopamine hydrobromide

ACE2 - angiotensin converting enzyme 2

AT-1 receptors - angiotensin II type I receptor

BP - blood pressure

bpm – beats per minute

BRS - baroreflex sensitivity

CFS - chronic fatigue syndrome

DA - dopamine

DBH - dopamine beta hydroxylase

DHPG - dihydroxyphenilglycol

DOPA - dihydroxyphenylalanine

HR – heart rate

HUT – head-up tilt table test

IST - inappropriate sinus tachycardia

MS - multiple sclerosis

NE - norepinephrine

NET - Norepinephrine transporter

NO - nitric oxide

OI – orthostatic intolerance

POTS – postural orthostatic tachycardia syndrome

PRA - plasma renin activity

RAAS - renin-angiotensin-aldosterone system

# SADRŽAJ

Sažetak

Summary

INTRODUCTION .....	1
EPIDEMIOLOGY .....	2
PATHOPHYSIOLOGY.....	2
Normal physiology of standing .....	2
Neuropathic.....	2
Hyperadrenergic.....	3
Genetic.....	4
Renin- angiotensin-aldosterone system and blood volume perturbation .....	4
Altered norepinephrine synthetic pathway.....	6
„The Grinch syndrome“ .....	6
CLINICAL MANIFESTATIONS .....	7
ASSOCIATED AND OVERLAPPING CONDITIONS.....	9
Chronic fatigue syndrome (CFS)/ Myalgic encephalomyelitis (ME).....	9
Multiple sclerosis .....	9
Inappropriate sinus tachycardia.....	10
Other .....	10
DIAGNOSTIC EVALUATION.....	10
MANAGEMENT.....	12
Nonpharmacotherapy.....	12
Pharmacological.....	13
PROGNOSIS.....	14
Zahvale.....	15
Literatura .....	16
Životopis .....	21

## **Sindrom posturalne ortostatske tahikardije**

Luka Crnošija, Ivan Adamec, Antonija Mišmaš, Mario Habek

### **Sažetak**

Ortostatska intolerancija se može opisati kao nemogućnost toleriranja uspravnog stava uz olakšanje simptoma nakon zauzimanja ležećeg položaja. Sindrom posturalne ortostatske tahikardije (POTS) je oblik ortostatske intolerancije definiran kao kontinuiran porast srčane frekvencije za  $\geq 30$  otkucaja u minuti ili kao porast frekvencije na vrijednost od  $\geq 120$  otkucaja u minuti unutar 10 minuta od početka stajanja ili head-up tilt testa uz pojavu simptoma ortostatske intolerancije i odsutnost ortostatske hipotenzije. Pacijenti kojima je dijagnosticiran POTS su uglavnom žene, s omjerom žena prema muškarcima 4-5:1, te starosti između 15 i 50 godina. Nekoliko patofizioloških mehanizama je moguće uključeno u razvoj POTS-a. Neki od njih su: distalna periferna neuropatija, poremećaji centralne kontrole simpatičkog živčanog sustava, oštećenje sinaptičkih mehanizama ponovnog unosa norepinefrina, poremećaji renin-angiotenzin-aldosteron osovine, promjene u sintetičkom putu norepinefrina. Najčešći simptomi povezani s POTS-om su omamljenost, presinkopa, slabost i palpitacije. Pogoršanje simptoma sa stajanjem i olakšanje nakon zauzimanja ležećeg položaja je karakteristično obilježje POTS-a. Pri postavljanju dijagnoze koriste se aktivni test stajanja i pasivni head-up tilt test, zajedno s detaljnom povijesti bolesti i kliničkim pregledom. Nefarmakoterapijski pristup liječenju POTS-a podrazumijeva povećan unos soli i vode te vježbanje. Farmakoterapija je usmjerena prema povećanju volumena tekućine, povećanju periferne vaskularne rezistencije i smanjenju centralne aktivnosti simpatičkog živčanog sustava. Velik broj pacijenata iskusi znatno poboljšanje nakon točno postavljene dijagnoze i pravilnog liječenja.

**Ključne riječi:** ortostatska intolerancija, sindrom posturalne ortostatske tahikardije, patofiziologija, neuropatski POTS, hiperadrenergički POTS, dijagnostika, terapija

## The postural orthostatic tachycardia syndrome

Luka Crnošija, Ivan Adamec, Antonija Mišmaš, Mario Habek

### Summary

Orthostatic intolerance(OI) can be defined as inability to tolerate upright posture relieved with recumbence. Postural orthostatic tachycardia syndrome(POTS) is a form of orthostatic intolerance defined as sustained increase in heart rate(HR) of  $\geq 30$  bpm or increase of HR to  $\geq 120$  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 female to male ratio of 4-5:1, and age range from 15 to 50. Several pathophysiological mechanisms are thought to underly POTS. Some of possible mechanisms are distal peripheral neuropathy, abnormalities of central control of sympathetic nervous system, impaired synaptic norepinephrine (NE) reuptake, renin-angiotensin-aldosterone axis disturbance and altered NE 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 characteristic POTS feature. Active stand test and passive head-up tilt table (HUT) test are used in diagnosing POTS, along with detailed history and examination. Non-pharmacological 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. Majority of patients experience substantial improvement, after correct diagnosis and suitable therapy.

**Keywords:** orthostatic intolerance, postural orthostatic tachycardia syndrome, pathophysiology, neuropathic POTS, hyperadrenergic POTS, diagnostics, therapy

## INTRODUCTION

Orthostatic intolerance(OI) can be defined as inability to tolerate upright posture relieved with 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. (Stewart 2012) Depending on the level of sympathetic activity patients with OI can be classified in two types. One type comprises patients with diminished symapthetic activity who develop hypotension during standing. This is acute in those with vasovagal syncope and chronic in patients with central or peripheral neurodegenerative diseases. In second type patients have increased sympathetic activity, without development of hypotension and with notable tachycardia as a response to orthostasis. Latter is referred to as postural tachycardia syndrome. (Kaufmann 2003)

The postural tachycardia syndrome (POTS) is a form of orthostatic intolerance defined as a sustained heart rate (HR) increment of  $\geq 30$  bpm (Freeman et al. 2011; Carew et al. 2009; Abed et al. 2012) or increase of heart rate to  $\geq 120$  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. (Freeman et al. 2011) Diehl proposes a surrogate criterion for diagnosing POTS in patients with typical symptoms but not fulfilling the HR increment of  $\geq 30$  bpm or HR  $\geq 120$  criterion as HR increase between minutes 5 and 10 of more than 8 bpm during head-up tilt test. (Diehl 2005)

The aim of this review is to investigate and summarize latest literature on postural orthostatic tachycardia syndrome.



## **EPIDEMIOLOGY**

POTS patients are mostly female, with female to male ratio of 4-5:1, and age range from 15 to 50 (Carew et al. 2009), but with relatively few patients over the age of 40 years. (Thieben et al. 2007) These demographics may be due to the effect of female sex hormones on adrenergic receptors sensitivity and norepinephrine (NE) metabolism. (Hart et al. 2011; Edgell et al. 2012) The true prevalence is not known, but is likely to be higher than 170 cases per 100,000. (Mathias et al. 2012)

## **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. (Carew et al. 2009) 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 mmHg). (Carew et al. 2009; Diehl 2005) It is important to notice that this reaction is swift and occurs within the first minute of assuming the upright position in normal subjects. (Diehl 2005)

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. (Jacob et al. 2000) examined sympathetic nervous system function by measuring norepinephrine-spillover

in response to three stimuli – cold pressor test, nitropruside and tyramine infusion. 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 patients. One study (Stewart 2002) shows that arterial vasoconstriction, which is normal response to orthostasis, is impaired in POTS patients. This finding is consistent with defective norepinephrine secretion. (Jacob et al. 2000; Stewart 2002) Carson et al. (Carson et al. 2001) made animal model of neuropathic tachycardia syndrome. 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. Vascular  $\alpha$ 1-sensitivity examined with selective agonist phenylephrine was also increased after administration of 6-OHDA. Latter finding is consistent with early work of Streeten (Streeten 1990) in which he describes hypersensitivity of feet veins to NE infusion typical of denervation. Distal sudomotor abnormalities can be found in approximately half of patients with POTS (Thieben et al. 2007; Peltier et al. 2010), although this finding does

not appear to correlate with symptom measurements. (Peltier et al. 2010)

Taking these findings into account it can be concluded that 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 (Diehl 2005) causing functional decline in circulatory volume, which results in a compensatory increase in HR and myocardial contractility. Neuropathic POTS is the most common form of POTS. (Kanjwal et al. 2011; Grubb 2008)

### **Hyperadrenergic**

Hyperadrenergic form of POTS is less frequent, encompassing about 10% of POTS patients. Patients with this form of POTS often display orthostatic hypertension, significantly elevated serum norepinephrine (>600 pg/mL) 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. (Carew et al. 2009; Kanjwal et al. 2011; Grubb 2008; Thanavaro & Thanavaro 2011) Some studies (Garland 2007; Lambert et al. 2008; Shannon et al. 2000) reported abnormally low concentration of plasma dihydroxyphenilglycol (DHPG), intraneural NE metabolite, in relation to NE concentration, providing evidence of impaired NE uptake. In some patients hyperadrenergic response may be compensatory reaction to hypovolemia or peripheral neuropathy with venous pooling. (Carew et al. 2009)

## **Genetic**

Norepinephrine transporter (NET) is presynaptic transporter responsible for the clearance of approximately 70% of synaptic NE. (Garland 2007) Heart is more sensitive to impairments in NE reuptake because cardiac sympathetic nerves recapture at least 80% of released NE. (Richard et al. 2012) Point mutation of gene encoding NET resulting in 98% loss of function has been recorded in one POTS patient. (Shannon et al. 2000) Two studies (Lambert et al. 2008; Richard et al. 2012) recorded reduced NET protein

expression in POTS patients. In work by Schroeder et al. (Schroeder et al. 2002) POTS-like phenotype was achieved in healthy subjects by administering 8mg of reboxetine, selective NET blocker. 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 (Lambert et al. 2008; Richard et al. 2012), except for tachycardia, which might be explained by failure of clearance of NE from cardiac sympathetic nerve synaptic spaces. (Richard et al. 2012)

## **Renin-angiotensin-aldosterone system and blood volume perturbation**

The renin-angiotensin-aldosterone system (RAAS) plays 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 ACE (angiotensin converting enzyme). 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 effect on plasma volume. (Raj et al. 2005; Mustafa et al. 2011; Stewart et al. 2006) Ang II is further degraded to Ang-(1-7) by ACE2 (angiotensin converting enzyme 2). 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. (Stewart et al. 2009) Ang II has various other effects besides already mentioned. Ang II is involved in a control loop as negative feedback to renin production. (Stewart et al. 2006) 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. (Mustafa et al. 2011) It can also increase the release of NE from ganglionic and postganglionic sympathetic nerves (Mustafa et al. 2011; Stewart et al. 2006) and inhibit NE reuptake in the nerve terminals with consequential effect on vasoconstriction. (Stewart et al. 2006) It also has direct

vasoconstrictive action by binding to AT-1 receptors on smooth muscle cells. Ang II has been shown to decrease bioavailable NO (nitric oxide). (Stewart et al. 2006) 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 (Richard et al. 2012; Raj et al. 2005; Mustafa et al. 2011; Stewart et al. 2006), a state sometimes referred to as 'renin-aldosterone paradox'. (Raj et al. 2005) In work by Raj et al. (Raj et al. 2005) patients with POTS had a mean plasma volume deficit of almost 350 mL. At least two studies (Stewart et al. 2006; Jacob et al. 1997) reported positive correlation between PRA and blood volume in POTS patients with low blood volume, when negative correlation would be expected. Several studies (Mustafa et al. 2011; Stewart et al. 2006; Mustafa et al. 2012) reported POTS patients with increased level of plasma Ang II. Mustafa et al. (Mustafa et al. 2012) reported blunted systemic vasopressor, but not renal vascular or adrenal secretory response to Ang II infusion in patients with POTS. This

study also reports 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. (Mustafa et al. 2012) hypothesise that high levels of Ang II could be explained by decreased ACE2 activity. This hypothesis is reinforced with findings of another study (Crackower et al. 2002) in which targeted disruption of ACE2 in mice resulted in increased Ang II levels. Work by Stewart et al. provides evidence for latter hypothesis, but they also hypothesise that defective ACE2 resulting in decreased levels of Ang-(1-7) might contribute to excessive vasoconstriction found in some POTS patients. (Stewart et al. 2006; Stewart et al. 2009) This subgroup of POTS patients are referred to as low-flow POTS patients. (Stewart et al. 2009)

This data suggest that defects in RAAS may play important role in 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 synthesised via tyrosine hydroxylation to DOPA (dihydroxyphenylalanine), DOPA decarboxylation to DA (dopamine). DA is then converted to NE through dopamine beta hydroxylase (DBH) action. Garland et al. (Garland 2007) measured DOPA and DA in POTS patients for the first time and found significantly increased level of DA, along with reduction in supine DOPA. Authors hypothesised that 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 study by Fu et al. (Fu et al. 2010) 27 POTS patients were submitted to autonomic function test, cardiac MRI and 19 patients completed 3-month exercise training program. 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 peak oxygen uptake, blood volume and plasma volume increased significantly. Ten out of 19 patients no longer met POTS criteria after training. The 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. Authors proposed new term for POTS to be „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 pathophysiological mechanisms mentioned here are

intertwined and that POTS is a result of their combination.

## **CLINICAL MANIFESTATIONS**

About half of patients with 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) antibody (Thieben et al. 2007; Kanjwal et al. 2011; Sandroni & Low 2009) in 15-25% of POTS patients. (Terlizzi et al. 2008) Some patients report that their symptoms begin after pregnancy, surgery, sepsis or trauma. (Mathias et al. 2012; Peltier et al. 2010; Kanjwal et al. 2011) On the other hand, patients with hyperadrenergic form of POTS often describe a more gradual and progressive appearance of symptoms over time rather than abrupt onset. (Grubb 2008; Shannon et al. 2000) One case report (Terlizzi et al. 2008) attributes the onset of reversible POTS to inadvertent overuse of Red Bull®. 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. (Grubb 2008)

Symptoms associated with POTS are numerous. Thieben et al. (Thieben et al. 2007) made retrospective study involving 152 POTS patients. 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. Kanjwal et al. (Kanjwal et al. 2011) retrospectively analyzed 27 patients with hyperadrenergic POTS and came over next results: 55-65% of patients reported symptoms of hyperadrenergic state in form of anxiety, tremulousness and excessive sweating; orthostatic palpitation was reported by 13(48,2%) and syncope by 11(40,7%) patients. About 30% of POTS patients have neurally mediated syncope. (Raj 2006)

Symptoms get worse with standing and are relieved with recumbence. (Raj 2006) Aggravating factors include heat or exercise (53,3%), post-prandial symptoms (23,7%), and worsening at time of menses (14,5%). (Thieben et al. 2007) 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. (Fu et al. 2010)

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 occurrence of 40-50% during standing. (Raj 2006) Other signs are rare and include pupillary dysfunction and symptoms consisted with peripheral neuropathy. (Carew et al. 2009)

## **ASSOCIATED AND OVERLAPPING CONDITIONS**

### **Chronic fatigue syndrome (CFS)/ Myalgic encephalomyelitis (ME)**

Overlapping between clinical manifestations of POTS and chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis, has been documented in literature. (Thieben et al. 2007; Jacob et al. 2000; Hoad et al. 2008; Okamoto et al. 2012) 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 between 48 and 77%, and CFS between 17 and 23%. (Jacob et al. 2000; Hoad et al.

2008; Okamoto et al. 2012) In work by Okamoto et al. (Okamoto et al. 2012) out of 47 POTS patients enrolled in the study 30(64%) fulfilled criteria for CFS. 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.

### **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. (Adamec et al. 2013a) In one prospective study (Adamec et al. 2013b) out of 112 patients diagnosed with relapsing remitting MS 21(18.8%) of them met the criteria for POTS. Seventeen of those patients were in relapse. Another study (Adamec et al. 2013a) conducted on large sample of patients, divided into group of 112 MS patients and group of 181 patients with symptoms of OI, showed that POTS is more frequent in MS patients in comparison with patients with symptoms of OI with no neurological



illnesses. Connection between MS and POTS is explained by the presence of demyelinating brainstem and hemispherical lesions which disrupt the physiological heart rate variability modulation. (Kanjwal et al. 2010)

### **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 (Carew et al. 2009), IST can be triggered by orthostasis and minimal exertion, (Morillo & Guzmán 2007) exaggerated response to isoproterenol infusion can also be seen in IST. (Grubb 2008) Although sometimes it can be challenging to differentiate between POTS and IST, there are some distinguishing features that can help in making 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 common finding in patients with IST. (Carew et al. 2009; Grubb 2008)

### **Other**

Migraine is found in about 42% of POTS patients. (Thieben et al. 2007) Joint hypermobility, irritable bowel syndrome, inflammatory bowel disease, mitral valve prolapse, and hypertension are frequently mentioned as co-morbidities associated with POTS. (Carew et al. 2009; Kanjwal et al. 2011; Thanavaro & Thanavaro 2011; Raj 2006) POTS patients are sometimes diagnosed with anxiety disorders, but that might be due to a misinterpretation of their physical symptoms. Patients with POTS often have diminished attention and concentration. (Raj 2006)

### **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, cardinal criterion in diagnosing POTS is HR increase of  $\geq 30$  bpm or increase

of heart rate to  $\geq 120$  bpm within 10 min of standing or head-up tilt associated with symptoms of orthostatic intolerance and absence of orthostatic hypotension. Two tests can be used to assess patient's reaction to postural change. Passive head-up tilt table (HUT) test (Figure 1) is the standard method, which consists of two phases. In the first phase patient is placed on tilt table for a period of 5-20 min in which supine HR and blood pressure (BP) is monitored. In the second phase patient is tilted to  $60^\circ$ - $80^\circ$  and HR and BP are measured periodically or continuously for 10-60min. (Carew et al. 2009; Abed et al. 2012; Thanavaro & Thanavaro 2011; Kanjwal et al. 2010; Plash et al. 2013) Test should be performed in a quiet, dimly lit, temperature-controlled environment. (Carew et al. 2009) Period of time spent in supine or tilted position depends on protocol used.

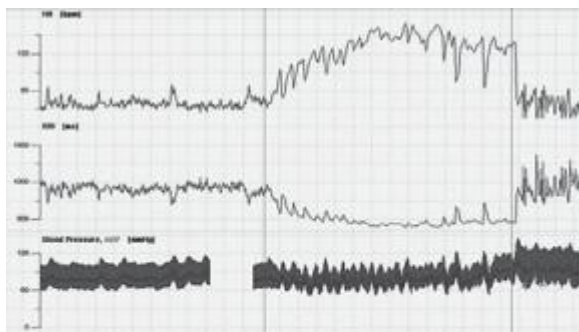


Fig. 1. An example of head-up tilt test in a patient with POTS: upper line shows continuous heart rate monitoring, lower line shows continuous blood pressure monitoring. Note the increase of heart rate after the tilt (first vertical red line)  $>30$  beats/minute, without fall in blood pressure.

Another test is active stand test, which is considered to mimic real life. Patient is asked to assume upright position following a period of time spent in supine position. Whilst patient is standing unassisted, HR and BP is measured periodically. (Carew et al. 2009; Abed et al. 2012; Raj 2006; Plash et al. 2013) Plash et al. (Plash et al. 2013) compared HUT to standing test in diagnosing POTS. In this study 10-min standing was the most accurate test, when using  $\geq 30$  bpm HR increment criterion. Results in this study suggest that 10-min tilt test is highly sensitive (93%), but has poor specificity (40%), when using the  $\geq 30$  bpm HR increment criterion. Plash et al. suggest that by increasing the HR criterion to 37 bpm 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  $\geq 6$  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 hyperadrenergic from neuropathic type

of POTS supine and standing serum NE levels should be obtained. A high standing NE (>600pg/mL) identifies patients with hyperadrenergic POTS, and predicts their response to  $\beta$ -blockade. (Thieben et al. 2007; Grubb 2008)

## 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. (Thanavaro & Thanavaro 2011) Patients should be taught three simple measures beneficial in improving orthostatic intolerance. The first measure is physical countermeasures. 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 consist of drinking

two 8-ounce ( $\approx$ 2 dL) glasses of water consecutively inducing sympathetically-mediated pressor response. (Low et al. 2009; Shannon et al. 2002)

## 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. (Carew et al. 2009; Grubb 2008) In one study (Fu et al. 2010) 10 out of 19 POTS patients that completed 3-month exercise training program no longer met the criteria for POTS. This and one other study (Winker et al. 2005) recorded increase in blood and plasma volume in patients who finished 3-month training program. Winker et al. (Winker et al. 2005) demonstrated that training can result in shift from sympathetic to vagal predominance which might be beneficial for patients with OI. Many patients with POTS are hypovolemic. These patients should increase salt intake up to 10-20 g per day and obtain 2-2.5 L of fluids per day. (Carew et al. 2009; Raj 2006; Low et al. 2009) Acute blood volume expansion by applying 1 liter of

physiological saline intravenously is highly effective in controlling the HR and acutely improving POTS symptoms, but the treatment is not practical on a day to day basis. (Carew et al. 2009; Raj 2006)

## **Pharmacological**

When nonpharmacological measures alone do not prove efficient, drugs are needed. (Mathias et al. 2012) The main goal of medications should be stabilization of the condition enough to enable POTS patients to undergo exercise training program. (Grubb 2008) Patients with neuropathic type of POTS are best treated with combination of fludrocortisone and  $\alpha$ -agonist midodrine. (Low et al. 2009) Daily dose of fludrocortisone should not exceed 300 $\mu$ g to avoid adverse effects. Initial dose of midodrine should be 2.5 mg, three times a day before meals and can be increase if needed to maximum recommended daily dose of 30 mg. (Mathias et al. 2012) Some patients have better response when midodrine is combined with acetylcholinesterase inhibitor pyridostigmine, at the dose of 60 mg 3 t.i.d. (Low et al. 2009) Pyridostigmine appears to be most effective in patients with postviral onset of POTS. (Grubb

2008) In patients who are unresponsive to above-mentioned therapy, selective serotonin reuptake inhibitor (SSRI) or norepinephrine reuptake inhibitor can be added. Octreotide administered by subcutaneous injection beginning at 50  $\mu$ g 2-3 times daily is an additional therapy for refractory patients. (Grubb 2008) Octreotide can be beneficial in patients with marked postprandial symptoms. (Mathias et al. 2012) Patients with hyperadrenergic form of POTS often respond best to agents that block norepinephrine or its effects. (Grubb 2008) Dual-acting  $\beta$ -blocker, such as carvedilol or labetalol, may be more effective than a pure  $\beta$ -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. two times a day respectively. (Thanavaro & Thanavaro 2011) Central sympatholytic medications, such as clonidine, is often used in patients with hyperadrenergic POTS. Clonidine, alpha 2 agonist, is administered orally or in the patch form 0.1-0.3 mg twice daily. (Mathias et al. 2012; Grubb 2008; Raj 2006) Ivabradine, sinus node blocker, is beneficial in some POTS patients. According to one retrospective case series (McDonald et al. 2011)

ivabradine appears to control symptoms associated with POTS with effectiveness similar to that of conventional treatment.

According to Thieben et al. (Thieben et al. 2007) most commonly prescribed medication are  $\beta$ -blockers (76.7%), followed by SSRI (51.7%), fludrocortisone (39.5%) and midodrine (31.6%).

## **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 combination of physical and pharmacological therapy, but patients with hyperadrenergic POTS will likely require therapy indefinitely. Majority of patients experience substantial improvement, after correct diagnosis and suitable therapy. (Grubb 2008; Sandroni et al. 1999; Sousa et al. 2012)

## **Zahvale**

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## **Životopis**

Rođen sam u Zagrebu 17. travnja 1990. Pohađao sam Osnovnu školu Julija Klović, a srednjoškolsko obrazovanje nastavio sam u V. gimnaziji. Nakon položene mature, 2008. godine upisao sam Medicinski fakultet Sveučilišta u Zagrebu. Od 2012. godine surađujem na raznim projektima pod vodstvom doc.dr.sc. Maria Habeka. Jedan od tih projekata predstavljao sam na International Congress of Clinical Neurophysiology u Berlinu 2014. godine.