Europace (2009) **11**, 18–25
doi:10.1093/europace/eun324

REVIEW

A review of postural orthostatic tachycardia syndrome

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Received 4 July 2008; accepted 4 November 2008

A 21-year-old female reports an 18-month history of light-headedness on standing. This is often associated with palpitations and a feeling of intense anxiety. She has had two black-outs in the past 12 months. She is not taking any regular medications. Her supine blood pressure was 126/84 mmHg with a heart rate of 76 bpm, and her upright blood pressure was 122/80 mmHg with a heart rate of 114 bpm. A full system examination was otherwise normal. She had a 12-lead electrocardiogram performed which was unremarkable. She was referred for head-up tilt testing. She was symptomatic during the test and lost consciousness at 16 min. *Figure 1* summarizes her blood pressure and heart rate response to tilting. A diagnosis of postural orthostatic tachycardia syndrome with overlapping vasovagal syncope was made.

Keywords Tilt table testing • Clinical features • Pathophysiology • Treatment • Postural orthostatic tachycardia syndrome

Introduction

Postural orthostatic tachycardia syndrome (POTS) is defined as a sustained heart rate increase of $\geq$30 bpm or increase of heart rate to $\geq$120 bpm within the first 10 min of orthostasis associated with symptoms of orthostatic intolerance[1–3] and without significant orthostatic hypotension (OH).

Patients with POTS are predominately female (4:1) and relatively young,[4,5] but can range in age from 15 to 50 years.[6] Differences in muscle sympathetic nerve discharge characteristics, in the setting of sympathetic fibre loss associated with POTS, may contribute to the predisposition to and greater prevalence of POTS in female individuals.[7]

There are no accurate epidemiological studies, but it is estimated that in the USA alone, there are millions of people affected by POTS.[8]

Pathophysiology

Normal physiology of standing

When supine, up to 30% of the blood volume is in the thorax. During orthostasis, 300–800 mL of blood is gravitated downwards from the thorax into the abdomen and lower extremities. Most of this pooling into lower limb veins occurs within 10 s. This causes a decrease in venous return to the right side of the heart with a subsequent reduction in the stroke volume and cardiac output. Arterial baroreceptors (carotid sinuses and the aortic arch) and cardiopulmonary mechanoreceptors (heart and lung) detect a reduction in pulse pressure and stroke volume. Compensatory reflexes lead to increased sympathetic nervous system output (peripheral arteriolar vasoconstriction) and reduced parasympathetic nervous system output (reduced vagal tone to the heart with cardio-acceleration). After orthostasis in normal subjects, there is a 10–15 bpm increase in heart rate, systolic blood pressure remains stable, and diastolic blood pressure usually increases (~10 mmHg).[9]

Postural orthostatic tachycardia syndrome

Postural orthostatic tachycardia syndrome is a clinical manifestation of multiple underlying mechanisms. It can be divided into a number of overlapping pathophysiological models as follows.

Neuropathic

This is thought to be associated with partial dysautonomia. The evidence in support of this is as follows:

- Distal anhidrosis of the legs is commonly found on thermoregulatory sweat testing and quantitative sudomotor axon reflex testing (up to 50% of POTS patients).[4,10]

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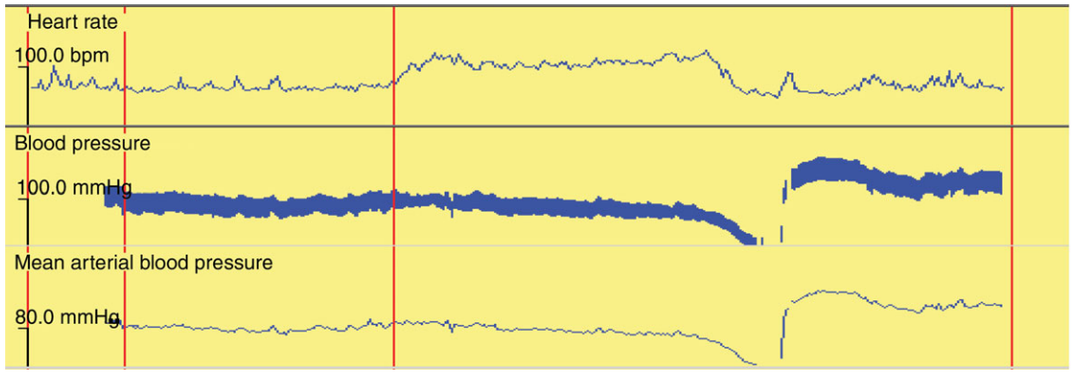

Figure 1 Blood pressure and heart rate response to tilt-testing in our patient. The reference arrows on the time axis indicate the onset of head-up tilt. Baseline heart rate pre-tilt was 72 bpm. The heart rate post-tilt was 114 bpm.

- Ganglionic acetylcholine receptor antibody is positive in between 10 and 15% of the cases.[4,11]
- There is a blunted increase in post-ganglionic sympathetic nerve discharge (muscle sympathetic nerve activity).[12] This peripheral abnormality might reflect partial dysautonomia. Astronauts returning from prolonged exposure to microgravity often display a form of orthostatic intolerance with features similar to POTS.[13] This is felt to be due to abnormal muscle sympathetic nerve activity.[14]
- It is shown that leg arteriolar vasoconstriction is impaired. Therefore, increased arterial inflow can enhance venous filling and cause venous pooling, despite the fact that venous capacitance is normal.[15]
- It has been shown that the increase in noradrenaline (NA) spillover in the legs is less during orthostasis in POTS patients compared with normal controls.[16]
- It has been shown there is excessive leg vein constriction in response to phenylephrine and NA infusion consistent with denervation hypersensitivity.[17]

Hyperadrenergic

Many patients complain of symptoms of sympathetic activation and often display orthostatic hypertension during tilting. Elevated standing serum catecholamine levels (NA $>$ 600 pg/mL) are relatively common in POTS subjects (29%).[4,12] It is postulated that this may occur due to excess systemic NA spillover, resulting from inadequate synaptic reuptake. Alternatively, there may be abnormalities with central control of the sympathetic nervous system, and it is shown that even when supine, POTS patients have augmented firing of cardiac sympathetic fibres.[12] In some subjects, this hyperadrenergic response may simply be a compensatory reaction to either hypovolaemia or peripheral dysautonomia with venous pooling.

Genetic

A gene mutation encoding the NA transporter protein has been described in patients with POTS phenotype.[18] This protein normally allows reuptake of NA from the synaptic cleft. Impairment in synaptic NA clearance can result in excessive sympathetic stimulation in response to physiological stimuli. Impaired clearance may also result in excess systemic NA spillover, providing a possible mechanism for increased systemic NA levels.

Hypovolaemic

Absolute hypovolaemia and a low red blood cell volume occur in POTS patients and aggravate symptoms of orthostatic intolerance.[4,19] Relative hypovolaemia can occur due to venous pooling and capillary leakage.[20]

Associated with this propensity to hypovolaemia in POTS is an abnormal physiological response to volume depletion. For example, it has been demonstrated that POTS patients lack the normal association between hypovolaemia and raised standing NA levels.[4]

The renin–angiotensin–aldosterone system has a major part in the neurohumoral maintenance of plasma volume. In normal subjects, hypovolaemia stimulates renin with subsequent increase in angiotensin II and aldosterone levels. These promote vasoconstriction and renal sodium and water retention. A low renin and aldosterone was found in hypovolaemic patients with orthostatic intolerance and POTS when the opposite would be expected.[19,21] This might contribute to impaired sodium retention and hypovolaemia. The sympathetic nervous system is a determinant of renal renin release; therefore, partial renal sympathetic denervation could explain low renin levels.

Impaired cerebral autoregulation

Postural orthostatic tachycardia syndrome patients have been found to have an excessive decrease in cerebral blood flow velocity during head-up tilt. It is controversial as to whether this decrease is due to an excessive sympathetic outflow to the cerebral vasculature or from hyperventilation.[22,23]

It is likely that each of the above models interact and that POTS is caused by a combination of these factors.

Clinical features

Onset

Development of POTS can vary from a rapid onset to an insidious progression of symptoms. Rapid onset has been reported post-operatively or after viral infections.[4]

Symptoms

The symptoms associated with POTS are myriad and can be divided into orthostatic and non-orthostatic types. There are also many non-specific symptoms, which often lead to difficulties with diagnosis. *Table 1* has been adapted from Thieben *et al.*'s paper.[4] This was a retrospective study of 152 patients attending the Mayo Clinic over an 11-year period. The group was predominantly female (86.8%) with a mean ± SD age of 30.2 ± 10.3 years.

Signs

The cardinal clinical sign in POTS is the presence of an abnormal tachycardia on the assumption of upright posture. Rarer physical signs include the development of acrocyanosis in 40–50% of the cases during prolonged standing.[5] Less common features on neurological examination in POTS patients include pupillary dysfunction (1.3%) and signs consistent with a peripheral neuropathy (1.4%).[4]

Aggravating factors

These include heat or exercise in 53.3% of the cases, post-prandial symptoms in 23.7%, and worsening at time of menses in 14.5%.[4]

Clinical overlap

There is an overlap between the clinical manifestations of POTS and chronic fatigue syndrome (CFS).[24,25] In particular, fatigue and reduced exercise tolerance can be prominent symptoms in both conditions.[4] There is evidence of POTS in adult CFS in 25–50% of the cases,[26–29] and a similar underlying dysautonomia may link both conditions.[25]

Inappropriate sinus tachycardia (IST) is a disorder characterized by an elevated resting heart rate that is out of proportion to physical demand and an exaggerated heart rate response to minimal exertion,[30] where secondary causes of sinus tachycardia have been excluded (*Figure 1*). There are many features of this condition that overlap with POTS including symptoms, abnormal heart rate response, and some underlying pathophysiological mechanisms.

There is a general agreement that IST is defined as a resting daytime heart rate greater than 90–100 bpm or a mean 24 h heart rate of greater than 90–95 bpm.[30–32] Electrocardiograph reveals sinus tachycardia.[33,34] Presenting symptoms are palpitations, fatigue, chest discomfort, exercise intolerance, and dizziness. This condition is more common in females.

Various underlying mechanisms for IST have been described, including augmented sinus node automaticity, autonomic dysregulation, and an abnormal baroreflex response.[33,35] Logically, beta-blockers seem a reasonable initial treatment option, but there is no evidence of efficacy in the literature. The role of sinus node ablation is controversial as a treatment option with varying reports of success. Ablation is predominantly associated with short-term symptomatic improvement. Long-term outcomes have been less favourable.[30,36,37] In patients with overlapping IST and POTS, sinus node ablation does not improve symptoms.[37]

There is a perception that anxiety may be more common in POTS subjects due to the overlap with somatic anxiety symptoms. However, two studies using the anxiety sensitivity index showed that POTS patients score within the normal range.[5,38]

There is disagreement in relation to co-existing OH. Some authors exclude a diagnosis of POTS if significant OH is present[18] with various levels of hypotension described, e.g. a decrease in systolic blood pressure (SBP) ≥10,[12] ≥20,[5,16] or ≥30 mmHg.[4,39] Some authors suggest OH can co-exist with POTS,[40] whereas others do not refer to OH in their definition.[2,41] It is reasonable to exclude significant OH (based on SBP reduction ≥30 mmHg) particularly when it is prolonged.

Some subjects fulfilling the typical clinical and heart rate criteria for POTS develop vasovagal syncope during tilt-table testing, with a 25% overlap reported.[42] It is likely that there are some similar pathophysiological features such as hypovolaemia that predispose to POTS, OH, and vasovagal syncope.

In one study, there was a higher than expected prevalence of mitral valve prolapse, irritable bowel syndrome, CFS, and inflammatory bowel disease.[43]

Table 1 Symptoms associated with POTS and their relative frequency in 152 patients

Symptom	Frequency (%)
Orthostatic	
Light-headedness or dizziness	77.6
Pre-syncope	60.5
Weakness	50
Palpitations	75
Tremulousness	37.5
Shortness of breath	27.6
Chest pain	24.3
Loss of sweating	5.3
Hyperhidrosis	9.2
Non-orthostatic	
Bloating	23.7
Nausea	38.8
Vomiting	8.6
Abdominal pain	15.1
Constipation	15.1
Diarrhoea	17.8
Bladder dysfunction	9.2
Pupillary dysfunction	3.3
Generalized	
Fatigue	48
Sleep disturbance	31.6
Migraine headache	27.6
Myofascial pain	15.8
Neuropathic pain	2

Adapted from Thieben *et al.*[4]

Diagnostic evaluation

This will begin with a detailed history and examination focusing on those symptoms and signs outlined earlier, which are suggestive of POTS. Consideration should be made also at this point for the identification of overlap syndromes and alternative explanations for the patient's presentation. Current guidelines also recommend supine and upright blood pressure measurements and 12-lead electrocardiography prior to tilt testing. In the event that any cardiological abnormalities have been identified at this point, the patient should undergo full cardiological assessment including echocardiography, stress testing, Holter monitoring, loop recording, and electrophysiological studies as appropriate.[44]

The cardinal diagnostic criterion for the diagnosis of POTS is the increase in heart rate following orthostatic stress. It is agreed that a sustained increase in heart rate of $\geq$30 or to $\geq$120 bpm within 10 min of orthostasis is diagnostic of POTS.[1–3] The orthostatic stressor of choice for the diagnosis of POTS is the automated tilt-table.[40] Continuous phasic haemodynamic blood pressure and heart rate recording using the Penaz technique[45] is now a widely accepted method of haemodynamic monitoring during the tilt test. The protocol for tilt testing varies. Current European Society of Cardiology Guidelines[44] suggests a tilt test involving a supine pre-tilt phase of at least 5 min when no venous cannulation is performed and at least 20 min when cannulation is undertaken. Tilt angle is specified at 60° to 70°. There follows a passive phase of head-up tilt lasting a minimum of 20 min and a maximum of 45 min. This should be performed in a quiet, dimly lit, temperature-controlled environment.

Further testing in the setting of POTS should be guided by findings in the history and examination, which are suggestive of an alternative cause for the patient's symptoms. Twenty-four hour ambulatory Holter-monitoring is not helpful in the setting of POTS unless IST is suspected as the underlying diagnosis.

Treatment

Both non-pharmacological and pharmacological interventions are useful in the management of POTS. However, the evidence base for many of these interventions is poor, and none of the pharmacological treatments that might help are licensed for use in POTS. They are summarized in *Table 2*.

Evidence-based treatment

Non-pharmacological

Water and salt

Salt supplements may be considered. Blood volume is low in many patients with POTS. The tachycardic response to upright posture correlates with the severity of hypovolaemia.[43,46] In a group of POTS subjects ($n = 9$), water ingestion did not affect standing blood pressure, but standing heart rate was lowered. It went from 123 ($\pm$23) bpm after 3 min of standing pre-water ingestion to 108 ($\pm$21) bpm post-water ingestion. However, the effects of water ingestion on symptoms in these patients were not reported.[47] Intravenous saline infusion decreased both supine and upright heart rate significantly.[43]

Table 2 Summary of treatment options existing for POTS with the corresponding levels of evidence

Treatment	Level of evidence
Non-pharmacological	
Water and salt supplementation	III
Exercise	Ib
Elastic support hosiery	IV
Pharmacological	
Fludrocortisone	III
Midodrine	IIb
Beta-blockers	III
Central sympatholytic agents	III
Pyridostigmine	IIb
Ivabradine	III
Octreotide	III
Erythropoeitin	III
ddAVP/desmopressin	IV
Selective serotonin reuptake inhibitors	IV
Methylphenidate	IV

Level of evidence: Ia, systematic review or meta-analysis of RCTs; Ib, at least one RCT; IIa, at least one well-designed controlled study without randomization; IIb, at least one well-designed quasi-experimental study; III, well-designed non-experimental descriptive studies, such as case–control or cohort studies; IV, expert opinion. Only the highest level of evidence has been selected for each modality.

Exercise

An exercise programme with regular aerobic exercise and lower limb resistance training may aid blood volume expansion and reverse deconditioning. In a randomized controlled trial, endurance exercise training (3 months jogging programme, increasing by 10 min duration each month, from 30 to 50 min, 3 times/week) improved symptoms of orthostatic intolerance in 31 POTS patients.[48]

Pharmacological

Fludrocortisone

Fludrocortisone is a potent mineralocorticoid. It promotes sodium and fluid retention and improves sensitivity of peripheral alpha-adrenergic receptors.[49] Fludrocortisone or bisoprolol or both improved the symptoms and haemodynamic abnormalities in a group of 11 patients with POTS.[50] Side effects include hypokalaemia, hypomagnesaemia, hypertension, and peripheral oedema.

Midodrine

Midodrine is an alpha-1 adrenoreceptor agonist and causes peripheral arterial and venous constriction. Midodrine improved symptoms and suppressed the heart rate response to tilting in 20 subjects with POTS.[51] In another similar study, midodrine (10 mg) suppressed the standing heart rate but did not alter the standing time of nine POTS subjects.[52] Midodrine (5–10 mg) reduced resting and upright heart rate significantly.[43] All these studies looked at acute and not long-term treatment. Another alpha-1 adrenoreceptor agonist, phenylephrine given intravenously to 14 patients with POTS, improved orthostatic intolerance and

suppressed heart rate increase when the subject was tilted to an angle of 35°.[53] Using strain gauge plethysmography, they showed that phenylepherine causes significant peripheral vasoconstriction and venoconstriction. Side effects include supine hypertension and piloerection.

Beta-blockers

Beta-blockers focus on sympatholysis. In 21 subjects with POTS, propranolol (single dose) reduced the resting heart rate and the immediate and 5 min heart rate responses to tilt but symptoms did not improve.[51] A case report showed that long-term propranolol (10 mg daily) was used successfully in the treatment of POTS and alleviated associated symptoms.[54] Esmolol, a beta-1 adrenergic antagonist (rapid onset and a very short duration of action), did not improve orthostatic intolerance or haemodynamics in 14 patients with POTS when given intravenously.[53] Dose-limiting side effects include fatigue and postural hypotension that could contribute to dizziness.

Central sympatholytic agents

Clonidine is an alpha-2 agonist that acts as a central sympatholytic agent. Long-term oral clonidine (0.3–0.4 mg daily) was tested in eight patients with POTS associated with mitral valve prolapse and orthostatic intolerance who were previously unresponsive to beta-blockers. Although there was no effect on orthostatic tachycardia, six of eight patients noted symptomatic improvement with clonidine (note no placebo control). There was an attenuated increase in standing NA level and total peripheral resistance with treatment.[55] Another study showed that clonidine (single dose of 0.1 mg) did not improve the orthostatic tachycardia[43] or symptoms and actually accentuated the reduction in blood pressure after tilt.[51]

Methyldopa increases alpha-2 receptor-mediated inhibition of the sympathetic nervous system. During one anecdotal study, six patients with POTS and concomitant mast cell activation disorder were contacted following 3 months treatment with anti-histamines and methyldopa, and a subjective clinical improvement in symptoms was documented.[56] These agents may cause drowsiness, dry mouth, or dizziness. Due to the effects on blood pressure, central sympatholytic agents should be reserved for patients exhibiting haemodynamic and symptomatic changes consistent with hyperadrenergic POTS. Although often recommended as treatment possibilities in expert reviews, there is very limited evidence base to support this; thus use should be limited to patients with refractory symptoms on a trial basis.

Pyridostigmine

The alternative approach of enhancing cardiac vagal tone using pyridostigmine has been studied. Pyridostigmine, an acetylcholinesterase inhibitor, enhanced parasympathetic activity and sympathetic ganglionic transmission, resulting in enhanced vascular adrenergic tone. Acute treatment with pyridostigmine (30–60 mg) significantly reduced postural symptoms and attenuated the postural tachycardia.[19,57,58] Procholinergic side effects include diarrhoea and excess salivation.

Ivabradine

Ivabradine, a sinus node blocker that selectively inhibits the I_f (funny) channel, reduces the firing rate of the sinus node without affecting blood pressure. A case study showed the benefits of ivabradine in a 15-year-old female with typical POTS, who did not respond to volume expansion and did not tolerate beta-blockers.[59] Ivabradine (titrated to 5 mg twice daily) caused a dramatic improvement in symptoms and a reduction in standing heart rate.

Octreotide

Octreotide is a somatostatin analogue, which has potent vasoconstrictive effects but must be given subcutaneously. Octreotide long-acting release 10–30 mg was studied in five patients with POTS or orthostatic intolerance. Orthostatic dizziness, chronic fatigue, and standing time improved and the postural tachycardia was suppressed.[60] The same group looked at nine patients with POTS and showed that octreotide (0.9 mcg/kg) suppressed the standing heart rate but did not alter the standing time.[52] Adverse effects include supine hypertension.

Erythropoietin

Erythropoietin is a growth factor that stimulates the production of red blood cells in the bone marrow, increasing red cell mass with a resultant increased central blood volume. Erythropoietin increases sensitivity to angiotension II with vasoconstrictive effects.[61,62]

Of eight POTS patients who were administered subcutaneous erythropoietin (50 U/kg, 3 times/week, for 6–12 weeks), six were found to have a low red blood cell volume before treatment. After treatment with erythropoietin, red blood cell volume improved but plasma volume did not increase. Although three patients reported an improvement in symptoms, overall there was no significant reduction in the orthostatic tachycardia.[63] This observational study provides little objective evidence of efficacy in POTS.

Erythropoietin is occasionally suggested in patients with refractory symptoms, where conservative or evidence-based approaches have failed.

Non-evidence-based treatments

Non-pharmacological

Elastic support hosiery

Waist high support hosiery may help improve venous return during orthostasis, but in practice are poorly tolerated and not aesthetically pleasing.

Pharmacological

ddAVP/desmopressin

Desmopressin is a synthetic form of anti-diuretic hormone enhancing reabsorption of water in the kidneys and leading to volume expansion. Side effects include hyponatremia, nausea, and headache.

Selective serotonin reuptake inhibitors (SSRIs)and selective noradrenaline reuptake inhibitors (SNRIs)

Efficacy of SSRIs in preventing neurocardiogenic syncope and OH has been demonstrated in a double-blind, randomized, placebo-controlled trial and various observational studies.[64,65] There is

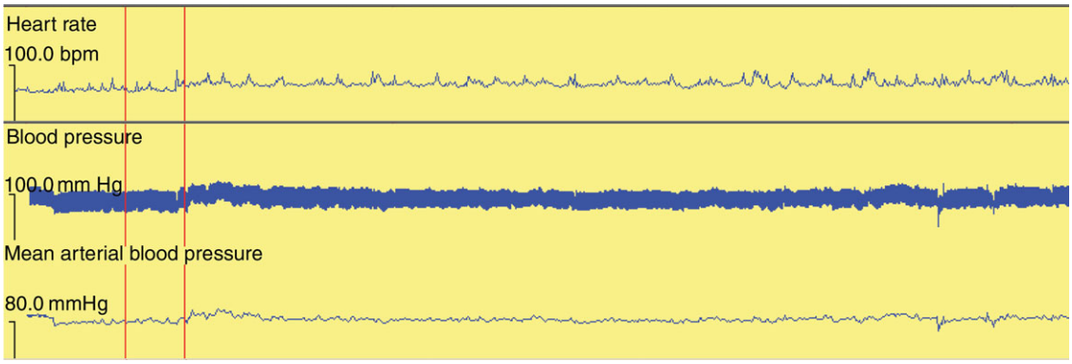

Figure 2 Blood pressure and heart rate response to tilt-testing following treatment. The reference arrows on the time axis indicate the onset of head-up tilt.

evidence that serotonin plays an important role in central control of both heart rate and blood pressure.[66] Despite SSRIs being documented as useful treatment option for POTS, this is anecdotal and there is no experimental evidence of efficacy.

There are similar anecdotal descriptions of efficacy for venlafaxine (a serotonin-NA reuptake inhibitor) without an evidence base. Conversely, there is documented evidence that the cardiovascular side effects include tachycardia, palpitations, OH, and an increase in mean arterial pressure.[67]

Reboxetine and sibutramine are SNRIs. In healthy subjects, these medications reduce tilt-induced syncope or pre-syncope and increase supine blood pressure, but are associated with a significant increase in heart rate pre- and post-tilting.[68,69]

Methylphenidate

Methylphenidate causes vasoconstriction by increasing presynaptic catecholamine release, decreasing reuptake, and inhibiting monoamine oxidase. Methylphenidate is suggested to reduce postural symptoms in POTS, but there is no evidence for this. There have been studies in which it has been used in vasovagal syncope.[70]

Discussion

Postural orthostatic tachycardia syndrome is a condition characterized by an abnormal persistent orthostatic tachycardia. Its pathophysiological basis is complex with multiple interacting models explaining its myriad manifestations. The most common symptoms include orthostatic dizziness, palpitations, weakness, tremulousness, and nausea. There are no specific abnormalities on clinical examination.

A detailed clinical evaluation should be carried out prior to head-up tilt testing to exclude other conditions, which may cause orthostatic intolerance. Overlapping conditions such as CFS and vasovagal syncope should also be considered during this initial evaluation. In the absence of clear guidelines for the diagnosis of POTS, we recommend following European Society of Cardiology Guidelines for the execution of tilt tests.[44]

It is important that this disorder is recognized, as some useful treatment options exist, but many suggested treatments have a poor evidence base. We suggest initial trials of non-pharmacological measures such as fluid expansion and avoidance of dehydration. In more severely symptomatic cases or in cases associated with vasovagal syncope, pharmacological intervention may be appropriate.

In the case presented earlier, our patient was advised to maintain adequate hydration at all times. She was encouraged to wear compression hosiery but declined. In the setting of previous syncope, she was trained in the use of counter-manoeuvres to avoid future vasovagal episodes. Due to the severity of symptoms, both she and her family were keen to progress to pharmacological measures and she was started on fludrocortisone at a dose of 0.1 mg/day. *Figure 2* summarizes the heart rate and blood pressure responses to head-up tilt post-treatment. She was no longer symptomatic.

Conflict of interest: none declared.

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