Case Report

# Sympathovagal balance analysis in idiopathic postural orthostatic tachycardia syndrome

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**Abstract.** The idiopathic postural tachycardia syndrome (POTS) is a complex disorder characterized by chronic orthostatic symptoms and an increase in heart rate within 10 minutes of standing on upright posture, without significant orthostatic hypotension. We describe a case of a 36 year-old patient with POTS, diagnosed by head-up tilt testing. Power spectral analysis of heart rate variability (HRV), performed during the tilt test, revealed the ratio of low and high frequency powers (LF/HF) that increased with the onset of orthostatic intolerance. The increase in LF/HF power ratio may represent sympathetic beta-receptors hyperactivity. Atenolol alleviated his clinical symptoms. (www.actabiomedica.it)

**Key words:** Postural orthostatic tachycardia sindrome (POTS), sympathovagal balance; heart rate variability (HRV), Head up tilt test

## Introduction

Orthostatic intolerance is defined by the inability to remain upright without severe signs and symptoms such as hypotension, tachycardia, lightheadedness, pallor, fatigue, weakness, and nausea. Orthostatic intolerance appears in many guises including overt dysautonomia, vasovagal syncope, and orthostatic tachycardia (1). Postural orthostatic tachycardia syndrome (POTS) is defined by the presence of symptoms of orthostatic intolerance associated with an increase in sinus heart rate of >30 beats/min or with a rate of >120 beats/min during the first 10 min of head-up tilt testing (HUTT) (2). We report a case of POTS in which we analyze sympathovagal balance during head up tilt testing and emphasize HUTT value in POTS diagnosis for patients with suggestive symptoms.

## Case report

A 36 year old man affected by arterial hypertension treated with ACE-inhibitor was referred to our hospital for palpitations and lypotimia. On several occasions, he experienced pre-syncopal symptomatology, especially in the morning while he was waking up and when he suddenly stood up after being in the sitting position, but syncope never developed. When he came to our observation, his body weight was 95 kg and his height was 170 cm. Physical examination was normal with blood pressure of 140/90 mmHg. Electrocardiographic examination (ECG) showed a sinus rhythm of 95 beats/minute without conduction abnormalities or ST-T changes. Neither chest x-ray nor echocardiografic examination revealed any cardiac abnormalities. Hematological examination, urinary analysis and thyroid function were all normal. Beck Anxiety Inventory score was 23. An atrio-ventricolar slow-fast node reentry tachycardia was initially suspected, due to his clinical presentation. This hypothesis was dismissed after electrophysiological transesophageus study.

We performed a head-up tilt test to evaluate his orthostatic intolerance. The tilt test was performed in a quiet room and in a fasting state. The ECG was continuously monitored and recorded to assess cardiac rhythm. Blood pressure was continuously monitored

with an arterial tonometer (Sure Sign V1 Electronics, Philips) placed on the left radial artery, calibrated against oscillometric sphygmomanometer pressure. A continuous electrocardiographic recorder (Holter monitor ELA medical SYNETEC) was also used for rhythm analysis. After resting for 10 min in the supine position, he was positioned upright at an 80 degree angle on a tilt table with a footboard for weight bearing. The passive tilt test was performed for a maximum of 45 min. His heart rhythm (HR) was 85 beats/min and blood pressure was 130/80 mmHg in the supine position. After 3 min of tilting, his HR bluntly increased to 150 beats/min and he began to complain of lightheadedness and weakness, but hypotension did not develop. At the end of the passive tilt test for 45 min, he had not experienced syncope or marked hypotension and when the patient returned to the supine position HR quickly came back to a normal value like at the beginning of the test. POTS diagnosis was made. Systolic and diastolic blood pressure values are shown in Figure 1.

In order to analyze the patient's sympathovagal balance during the head-up tilt testing, power spectral analysis of heart rate variability (HRV) was performed using the ELA medical SYNETEC version 1.10 monitoring system. Spectral indices of HR variability were computed by Fast Fourier analysis for each 2-min interval with 1-min overlap during the passive tilt test. The power spectrum was calculated as high frequency (HF, 0.15–0.40 Hz), low frequency (LF, 0.05–0.15 Hz), and as the ratio of LF to HF power (LF/HF). The changes in HF and LF/HF during the tilt test are shown in Figure 2. The HF component value decreased at the beginning of tilting and remained low during the test. The LF/HF tended to fluctuate, but it reached a higher level after 35 min of tilting when the patient began to experience symptoms of orthostatic intolerance. He started therapy with atenolol 100 mg every morning. We suggested losing weight and increasing fluid intake about every three hours during the day. His symptoms of orthostatic intolerance resolved after approximately thirty days.

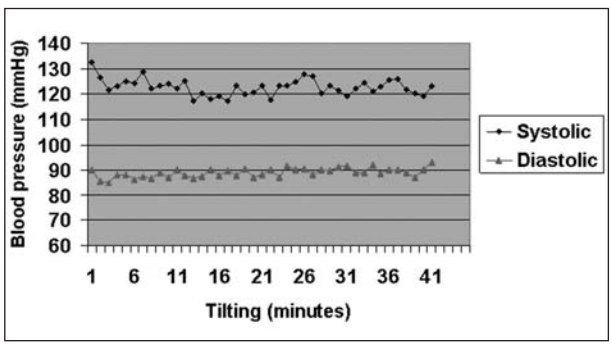


**Figure 1.** Changes in systolic and diastolic blood pressure during the passive tilt testing.

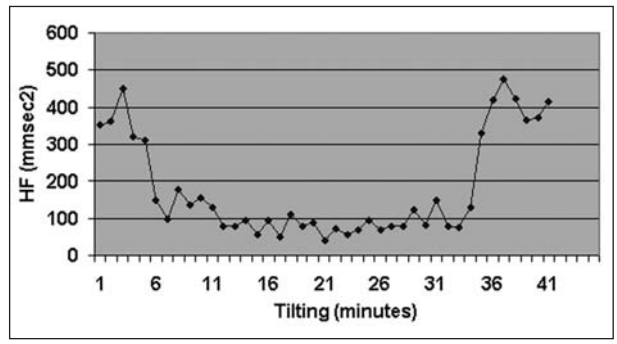


**Figure 2.** Changes in high-frequency (HF) power during the passive tilt testing.

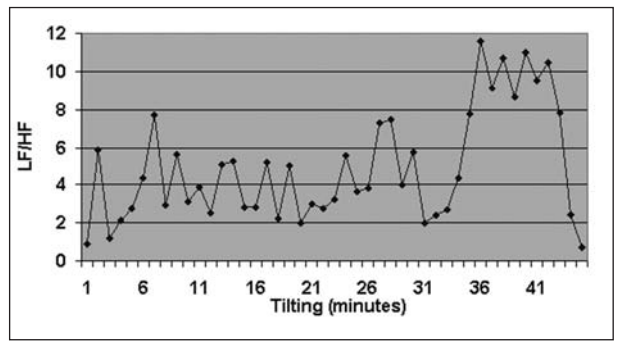


**Figure 3.** Changes in the ratio of low-frequency (LF) to HF power (LF/HF) during the passive tilt testing.

## Discussion

*Background*

POTS has been described since 1940 and is usually defined as the development of orthostatic symptoms associated with at least a 30 beat/minute increase in HR or a HR of =/>120 beats/ minute, that occurs within the first 10 minutes of standing without

orthostatic hypotension (2). Patient's age range is 10/60 years. HUTT is the gold standard for POTS diagnosis and it is also useful for differential diagnosis between POTS and neurally mediated syncope (3, 4). In this case report we showed the HRV dynamic changes during tilt testing in a POTS patient in order to analyze sympathovagal balance and better understand POTS physiopathologic mechanism.

*Heart Rate Variability (HRV) analysis*

HRV is a non invasive electrocardiographic marker reflecting the activity of the sympathetic and vagal components of the autonomic nervous system on sinus node function. It expresses the total amount of variations of instantaneous HR (5, 6). Thus, HRV analyzes the tonic baseline autonomic function. A predominance of sympathetic tone in cardiac activity induces tachycardia and reduced beat-to-beat variations, whereas parasympathetic nerve activity reduces heart rate and increases HRV (7). Spectral analysis of heart rate variability has been used to explore dynamic mechanisms in the cardiovascular system and appears to provide a quantitative evaluation of the sympathovagal interaction that modulates cardiovascular function (8). It has been shown that harmonic oscillations in heart rate are concentrated into at least two distinct bands. The one referred to as the low frequency (LF) band is affected by the oscillatory rhythm of the baroreceptor system and is thought to be mediated by both sympathetic and parasympathetic influences. The high frequency (HF) band, has respiration as the primary rhythmic stimulus and is mediated by changing levels of parasympathetic tone. Heart rate variability involves a complex interaction between several mechanisms working to maintain heart rate and blood pressure within normal limits. The LF/HF ratio is a useful parameter that reflects the balance of autonomic nervous activities (9). The normal heart rate behaviour during tilt involves an early rise, with an immediate increase predominantly caused by withdrawal of the vagal tone, and a more delayed increase over the first two minutes caused by enhanced sympathetic activity (10). The subsequent heart rate showed a smaller progressive rise throughout the duration of a variety of tilt protocols. Increased LF power and decreased HF power, as well as an increased sympathovagal balance, reflect the normal response to upright tilt. In our patient, LF/HF tended to fluctuate during tilt, but increased in parallel with the development of orthostatic intolerance without any changes in the HF value. No significative change in blood pressure has been showed. The increase in LF/HF power ratio may represent a sympathetic beta-receptor hyperactivity, that may occur as a result of selective sympathetic neuropathy leading to excessive peripheral pooling of blood on assuming the upright position.

*POTS physiopathology*

Multiple distinct pathophysiological subtypes within the postural tachycardia syndrome (POTS) are shown, including neuropathic POTS and central hyperadrenergic POTS. In neuropathic POTS there is patchy denervation of the sympathetic innervation of the blood vessels in the extremities (especially the legs) and the kidney with subsequent hypovolemia and increased orthostatic venous pooling. This feeds back to the brain to increase sympathetic nervous system outflow in a compensatory effort. This increased sympathoneural flow is sensed mostly in the heart where no denervation is present. Onset may occur after a viral infection, trauma, or surgery or may be associated with the joint hypermobility (11).

In central hyperadrenergic POTS, the underlying problem appears to be an excessive sympathetic nervous outflow from the brain that affects the blood vessels, kidneys and the heart; in addition to tachycardia, this form of POTS is often associated with orthostatic hypertension syndrome. In this form, there is believed to be an inadequate feedback process that arises from above the level of the baroreflex. Recently, an increased noradrenergic tone at rest and a blunted postganglionic sympathetic response to standing with compensatory cardiac sympathetic overactivity has been proposed (12). Recent genetic studies have demonstrated that a defective gene causes a dysfunction in a norepinephrine transporter protein, producing excessive serum norepinephrine levels. Impairment of synaptic norepinephrine clearance may produce a state of excessive sympathetic activation in response to physiologic stimuli (13). According to Schondorf et al.

attenuated post-viral panautonomic neuropathy could also represent another cause of dysautonomia (14). Although no previous viral illness was identified in our patient, beta-receptor hypersensitivity may have played an important role in his orthostatic intolerance since this symptom was alleviated by beta-blocker administration.

*POTS diagnosis*

Tilt table testing is useful as a standardized measure of response to postural change in patients with dysautonomic alteration (4). In our patient, POTS diagnosis before HUTT was not easy because the orthostatic intolerance symptoms were compatible whit neurally mediated syncope. Morever a considerable overlap in the symptoms between POTS and neurally mediated syncope has been shown; POTS symptoms (blunted postural tachycardia, disabling fatigue, light-headedness, dizziness) are never associated with significant blood pressure changes in contrast with neurally mediated syncope patients, in which hypotension is usually present; it may probably be due to different degrees of reflex neural inhibition (15). In POTS, tachycardia induces a partial and selective reflex inhibition of muscle sympathetic nerve activity and blood pressure is maintained by the faster HR. In neurally mediated syncope, postural change may elicit a stronger neural inhibitory reflex that causes hypotension and bradycardia.

*POTS therapeutic management*

No therapy is considered as successful for all patients with POTS. Initial efforts should focus on identifying and treating any reversible causes. Contributory medications, especially vasodilators or diuretics, should be withdrawn and the treatment should be optimized for any chronic disease. It is important to educate the patient and his family on the nature of the disorder. Changing daily life style, weight loss, mild aerobic exercises, alcohol excess avoid and dehydration hypovolemia prevention whith fluid intake increase, sleeping with the head of the bed slightly elevated or resistance training to build up the lower extremities may help relieve the severity of POTS symptoms (16, 17). There are no pharmacological agents for POTS therapy that have been tested in a long-term properly powered randomized clinical trial. Central sympatholytic agents, such as clonidine (18), or beta-adrenergic antagonists, like propanolol, are often useful and well tolerated for POTS treatment, especially if used in low doses in patients with central hyperadrenergic POTS. Methyldopa, a false neurotransmitter, is sometimes more successful in controlling symptoms in these patients at doses of 125 mg to 250 mg (19). Midodrine and octreotide suppressed tachycardia in POTS and improved standing times in orthostatic intolerance; both peripheral alpha-1 receptor antagonists showed similar potencies and combination therapy was not significantly better than monotherapy (20). Acute acetylcholinesterase inhibitors, like pyridostigmine, significantly attenuated tachycardia in POTS. Morever an improvement in symptom burden with this promising therapy has been observed (21). Several studies have shown a disturbance of central serotonin production and regulation in patients with POTS and other syndromes of autonomic dysfunction (22). The selective serotonin reuptake inhibitors (SSRIs) have a role in the treatment of selected patients with POTS, and venlafaxine is probably more effective than other SSRIs; however, any other agent in this class may be effective. There is some limited experience with phenobarbital in POTS patients (1).

In the partial dysautonomic form fludrocortisone, a mineralocorticoid may be used. It acts on the distal tubule causing reabsorption of sodium in exchange of potassium and hydrogen. This leads to water retention, thereby expanding volume, but sometimes at the cost of hypokalemia. This drug not only expands volume, but also appears to sensitize peripheral alfa 1-adrenergic receptors to the patient's own catecholamine (23). Frequently patients will require a combination of various therapies to be effective. All therapies used are shown in Table 1. In our patient atenolol 100 mg every morning improved his symptoms in approximately thirty days.

*Limitation*

Plasma norepinephrine levels in both supine and standing position was not measured. The supine nore-

**Table 1.** Treatment Options

| Therapy | Dose |
|---|---|
| Head-up tilt of bed | 45° Head-up tilt of bed (often will need footboard) |
| Elastic support hose | Requires at least 30-40 mm Hg ankle counterpressure, works best if waist high |
| Diet | Fluid intake of 2-2.5 L/d Na intake of 150-250 mEq/d |
| Exercise | Aerobic exercise (mild) may aid venous return; water exercise particularly helpful |
| Clonidine | 0.1-0.3 mg PO BID or patches placed 1/wk |
| Metoprolol | 25-50 mg PO BID to TID |
| Methyldopa | 125-250 mg PO |
| Midodrine | 2.5-10 mg every 2-4 hours; may use up to 40 mg/d |
| Octreotide | 25 μg SC BID, may titrate to 100-200 μg TID |
| Pyridostigmine | 60 mg PO BID |
| Venlafaxine | 75 mg XR form PO QD or BID |
| Paroxetine | 10 mg PO QD |
| Fludrocortisone | Begin at 0.1-0.2 mg/d may work up to doses not exceeding 1.0 mg/d |

PO indicates by mouth; BID indicates twice daily; TID, three times a day; and QD, every day

pinephrine is often normal in patients with POTS, while the upright norepinephrine is usually elevated, a reflection of the exaggerated neural sympathetic tone that is present in these patients while upright. Standing plasma norepinephrine ≥ 600 pg/ml (≥ 3.5 nM) is one criterion for defining POTS (24).

## Conclusion

This case report underlines usefulness of head-up tilt testing in differentiating POTS from neurally mediated syncope in a patient with orthostatic intolerance. The HRV measure during HUTT in a patient with POTS studies the sympathovagal balance. This analysis confirms a strongly activated sympathetic tone during a passive tilt with concomitant development of orthostatic intolerance in our patient.

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