The Postural Orthostatic Tachycardia Syndrome: A Neurocardiogenic Variant Identified During Head-Up Tilt Table Testing

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GRUBB, B.P., ET AL.: The Postural Orthostatic Tachycardia Syndrome: A Neurocardiogenic Variant Identified During Head-Up Tilt Table Testing. *Head upright tilt table testing has emerged as an accepted modality for identifying an individual's predisposition to episodes of autonomically mediated hypotension and bradycardia that are sufficiently profound so that transient loss of consciousness ensues (neurocardiogenic syncope). However it has also become apparent that less dramatic falls in blood pressure, while not sufficient to cause full syncope, may produce symptoms such as near syncope, vertigo, dizziness, and TIA-like episodes. We have identified a subgroup of individuals with a mild form of autonomic dysfunction with symptoms of postural tachycardia and lightheadedness, disabling fatigue, exercise intolerance, dizziness, and near syncope. During baseline tilt table testing these patients demonstrated a heart rate increase of ≥ 30 beats/min (or a maximum heart rate of 120 beats/min) within the first 10 minutes upright (unassociated with profound hypotension), which reproduced their symptom complex. In addition these patients exhibit an exaggerated response to isoproterenol infusions. Similar observations have been made by others who have dubbed this entity the Postural Orthostatic Tachycardia Syndrome (POTS). We conclude that POTS represents a mild (and potentially treatable) form of autonomic dysfunction that can be readily diagnosed during head upright tilt table testing. (PACE 1997; 20[Pt. I]:2205–2212)*

autosomic dysfunctions, chronic fatigue, tilt table testing

Introduction

Transient periods of neurocardiogenically mediated hypotension and bradycardia have become a well-recognized cause of recurrent syncope.[1] The use of tilt table testing as a method of provoking these episodes has not only allowed for a better diagnosis of this condition, but also permitted a better understanding of the nature of the disorder.[2] During these investigations it became evident that transient alterations in autonomic tone could produce varying degrees of hypotension, that although not profound enough to result in full loss of consciousness, were nonetheless sufficient to produce symptoms such as vertigo, lightheadedness, near syncope, and transient ischemic attacks.[3,4] In the course of these investigations we have identified a subgroup of individuals who have a milder form of orthostatic intolerance who may present with complaints of orthostatic lightheadedness, postural tachycardia, disabling fatigue, exercise intolerance, dizziness, or near syncope. More detailed evaluations of these individuals revealed that the histories, physical findings, and responses to tilt table testing were all essentially similar. Others have also made similar observations and have dubbed this entity the Postural Orthostatic Tachycardia Syndrome (POTS).[5,6] The present study describes the clinical presentation of these patients, their responses to head upright tilt table testing, and the outcomes of pharmacological therapy.

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Methods

A total of 28 patients were identified for inclusion in this evaluation. Patients were included in the analysis if they had a 6 month or greater history of orthostatic intolerance manifested by orthostatic tachycardia, weakness, lightheadedness, fatigue, and near syncope. Patients who had experienced full clinical syncope (the transient complete loss of consciousness with spontaneous recovery) were not included in this study. Patients who were on chronic antihypertensive, diuretic, anticholinergic, or antidepressant medications, those with diabetic neuropathy or multisystem disease of any etiology were excluded, as were any patients who had been immobile for prolonged periods. Each patient had undergone a thorough history and physical examination as well as detailed blood chemistry analysis and thyroid profile analysis. Twenty-four patients underwent two-dimensional and Doppler echocardiography. Sixteen patients had undergone either computed axial tomography (CT) or magnetic resonance imaging (MRI) of the brain at the time of referral. Seven patients had undergone electrophysiological studies prior to referral. Ambulatory ECG (Holter) monitoring had been performed in 29 patients prior to referral.

Each of the patients underwent head upright tilt table testing, which was performed in the fasting state. All cardioactive medications were terminated > 5 half-lives before the study. Each patient was connected to a standard cardiographic monitor for continuous evaluation of heart rate and rhythm, and a standard sphygmomanometer was used for blood pressure measurements. After baseline determinations of heart rate and blood pressure were made, each patient was positioned at an angle of 80° from horizontal for up to 45 minutes on a tilt table with a foot board made for weight bearing. Blood pressure measurements were obtained every 3 minutes, and ECG monitoring was performed continuously. The patient was continued upright for the entire 45-minute period. A positive test was defined as one which reproduced the patient's symptom complex. If the patient remained asymptomatic throughout the course of the test the patient was lowered to the supine position and an intravenous infusion of isoproterenol was begun at 1 μg/min. The supine heart rate response was noted and the dose was then titrated to achieve a stable heart rate 20% above the supine resting heart rate. Head upright tilt table testing was then performed as before for a period of 20 minutes. Five patients underwent a second diagnostic tilt table study using the above protocol on a different day.

Therapeutic Trials

Each of the patients in whom tilt table testing reproduced their symptoms received medical therapy in an attempt to lessen the severity of their symptoms. The agents used were selected based on our experience in treating other autonomic disorders, such as neurocardiogenic syncope and orthostatic hypotension.[7] The following agents were use: fludrocortisone 0.1-mg po bid; atenolol 50-mg po qd; the serotonin re-uptake inhibitors sertraline hydrochloride 50-mg po qd or nefazodone hydrochloride 150-mg po bid; and erythropoietin (epoetin alpha) 50 u/kg three times weekly.[8] In one patient, methylphenidate 10-mg po tid was used. Not all drugs were tested in every patient.

Results

Of the 28 patients evaluated, there were 26 women and 2 men. The mean age of the patients was 30 ± 12 years (range 14–56 years). CT and MRI scans were normal in all of the patients who underwent them. Seven of the 24 patients who underwent echocardiograms were felt to have mitral valve prolapse, but were otherwise normal. Electrophysiological studies were normal in the seven patients who underwent them. Blood chemistry analysis as well as thyroid status were normal in all patients, as were complete blood counts. Sixteen patients had undergone previous endocrinological evaluation for possible conditions such as hypoglycemia, carcinoid syndrome, pheochromocytoma, and mastocytosis, all of which were negative.

The symptoms experienced by this group of patients are listed in Tables I and II. These included orthostatic tachycardia (80%), lightheadedness after 5–10 minutes upright, easy fatigability (80%), vertigo or dizziness (50%), exercise intolerance (65%), cognitive impairment (40%), and near syncope (70%). The mean duration of symptoms was 14.6 ± 6.5 months (range 6–30

Table I.

Patient Characteristics

Patient	Age (yrs)	Sex	Appr. Symptom Duration	Three Principle Complaints			Potential Precipitating Event
1	16	F	6 months	O.T.	Fatigue	N.Sync.	Post viral
2	32	F	24 months	O.T.	Fatigue	E.I.	Post partum
3	30	F	21 months	O.T.	Fatigue	N.Sync.	Post viral
4	45	F	6 months (intermittent—8 yrs)	N.Sync.	Fatigue	C.I.	—
5	35	F	12 months worse (intermittent—10 years)	O.T.	Fatigue	C.I.	—
6	18	F	12 months	O.T.	Fatigue	C.I.	Post viral
7	26	F	18 months	Fatigue	C.I.	O.T.	Post partum
8	38	F	9 months	C.I.	N.Sync.	O.T.	Post traumatic
9	19	F	14 months	N.Sync.	Dizzy	O.T.	Post viral
10	55	M	15 months	N.Sync.	C.I.	O.T.	Post viral
11	14	F	20 months	N.Sync.	C.I.	Dizzy	Post viral
12	18	M	12 months	C.I.	Fatigue	N.Sync.	—
13	57	F	26 months	Fatigue	C.I.	N.Sync.	—
14	17	F	8 months	Fatigue	N.Sync.	Dizzy	—
15	29	F	12 months	O.T.	Fatigue	—	—
16	52	F	28 months	O.T.	N.Sync.	C.I.	Menopause
17	35	F	14 months	O.T.	N.Sync.	E.I.	—
18	19	F	20 months	N.Sync.	Fatigue	C.I.	—
19	54	F	30 months	N.Sync.	O.T.	Fatigue	Post-sepsis
20	29	F	16 months	C.I.	Fatigue	N.Sync.	Post viral
21	34	F	9 months	O.T.	N.Sync.	E.I.	—
22	29	F	18 months	Fatigue	E.I.	N.Sync.	—
23	37	F	12 months	Fatigue	E.I.	N.Sync.	—
24	32	F	7 months	Fatigue	O.T.	E.I.	—
25	17	F	10 months	Fatigue	C.I.	N.Sync.	—
26	19	F	14 months	N.Sync.	O.T.	Fatigue	—
27	25	F	6 months	Fatigue	N.Sync.	C.I.	—
28	24	F	12 months	N.Sync.	Fatigue	Dizzy	—
Mean	30.5		14.7				
Std Dev.	12.4		6.6				

C.I. = Cognative impairment; E.I. = Exercise intolerance; N.Syn. = Near Syncope; O.T. = Orthostatic Tachycardia.

Table II.

Total Percentage of Patient Group Complaining of a Particular Postural Symptom

Tachycardia/Palpatation	70%	Cognative Impairment	40%
Fatigue	80%	Visual Blurring	30%
Exercise Intolerance	65%	Gastric Dysmotility	10%
Lightheadedness/dizziness	50%	Chest Wall Pain	20%
Near Syncope	70%	Anxiety	25%

months). Many felt unable to complete their occupational duties or usual household tasks. In seven patients the symptoms were acute in onset and in each followed a severe "flu-like" illness characterized by fever, cough, and gastrointestinal onset. The remaining patients reported a long history of symptoms that in some extended to adolescence. Two patients reported that their symptoms began after pregnancy. One patient said symptoms began after a motor vehicle accident and one patient after sepsis associated with gallbladder disease. Each of the patients felt that their symptoms were extremely limiting to them and over half felt them disabling in nature.

Interestingly, 18 of the patients gave a history of intermittent constipation, and of these, 3 had complaints of postprandial bloating and 1 of vomiting. Two of these patients were later (after tilt table testing) seen by the gastroenterology service and were found to have delayed gastric emptying. Six patients gave a history of extreme tachycardia, flushing, and lightheadedness following meal ingestion.

Responses to Head-Up Tilt Table Testing

The responses to head-up tilt table testing are seen in Table III. Upon the assumption of upright posture during the baseline tilt, each of the patients demonstrated an increase in heart rate of at least 30 beats/min and in each case the heart rate exceeded 110 beats/min within 10 minutes of being positioned upright. Concomitant with the increase in heart rate was a mean fall in systolic blood pressure of approximately 20 mmHg, although in no patient did the systolic blood pressure fall below 85–90 mmHg. Each patient began to experience symptoms similar to those experienced clinically during tilt. Although seven patients became near syncopal during the time of the tilt, no patient experienced complete loss of consciousness. The two patients later shown to have delayed gastric emptying complained of extreme nausea during tilt.

The response of the majority of this group to a low dose of isoproterenol was striking, demonstrating an exaggerated heart rate increase with a mean value of 32 beats/min (the usual upper limit of normal is reported as approximately 15 beats/min).[9] Interestingly, only three of these patients complained of profound anxiety or tremulousness (symptoms that usually are seen in patients with hyper β-adrenergic states).[10]

Concomitant with the development of tachycardiac and pressure drop during the baseline tilt, the lower limbs and feet of three patients were seen to darken to a deep blue, suggesting the possibility of considerable venous pooling.[11] In the five patients who underwent a second diagnostic tilt study, the findings of the first study were reproduced.

Responses to Therapy

Seven patients responded to therapy with fludrocortisone alone. Three patients responded to a combination of fludrocortisone and atenolol (two of whom had exaggerated responses to isoproterenol associated with symptoms), and one to atenolol alone. Two patients responded to the combination of sertraline and fludrocortisone and five patients to the combination of nefazodone and fludrocortisone. One patient responded to a combination of methylphenidate and fludrocortisone. Two patients responded to therapy with erythropoietin alone (after proving intolerant or unresponsive to other therapies). Five patients proved unresponsive to (or intolerant of) all attempts at therapy. Two patients were lost to follow-up. Of the 21 patients who responded to one of the above mentioned therapies (over a mean follow-up period of 16 ± 9 months), 7 reported a moderate (but significant) reduction in symptoms, 10 reported a marked reduction in symptoms, and 4 reported near elimination of symptoms.

Discussion

In the course of our investigations into patients with recurrent syncope due to transient alterations in autonomic tone resulting in hypotension and bradycardia (neurocardiogenic syncope), we have become aware of a group of individuals who seem to suffer from a mild form of autonomic imbalance. Although these individuals do not experience true syncope (the transient loss of consciousness with spontaneous recovery), they do exhibit a range of sometimes disabling symptoms that include signs of orthostatic intolerance, such as postural lightheadedness, tachycardia and palpitations, visual blurring or tunneling, dizziness,

Table III.

Response to Head-Up Tilt in Patients with POTS

Patient	HR Supine	Maximum HR in 1st 10 Min	BP Supine mm Hg	BP at Max HR mm Hg	Increase in Supine HR to 1 μg/min Iso in bpm	Effective Therapy
1	72	117	115/70	110/60	40	none
2	100	145	130/80	95/50	32	Atenolol Fludrocortisone
3	80	132	120/75	115/90	27	none
4	75	120	130/80	126/75	51	Sertraline Fludrocortisone
5	55	98	100/95	95/70	19	Fludrocortisone
6	86	130	105/60	115/74	24	none
7	93	138	140/90	95/65	30	Sertraline Fludrocortisone
8	91	140	107/55	95/70	15	none
9	95	130	125/85	100/60	22	none
10	66	111	95/50	95/75	37	Fludrocortisone
11	92	132	138/93	126/84	26	none
12	64	144	102/69	120/70	51	Atenolol Fludrocortisone
13	88	136	130/67	90/68	46	Nefazodone Fludrocortisone
14	83	160	115/60	98/70	36	Atenolol Fludrocortisone
15	74	109	111/70	100/75	38	Nefazodone Fludrocortisone
16	65	100	95/60	90/78	23	Fludrocortisone
17	69	100	111/63	148/86	53	Nefazodone Fludrocortisone
18	91	125	107/65	100/80	12	Fludrocortisone
19	92	128	140/80	120/70	21	Nefazodone Fludrocortisone
20	64	110	102/60	90/70	29	Fludrocortisone
21	72	118	126/71	110/90	48	Erythropoietin
22	89	122	140/85	145/95	30	Atenolol
23	78	109	95/60	90/60	39	Fludrocortisone
24	81	117	104/70	92/56	22	Erythropoietin
25	76	115	100/64	90/65	28	Methylphenidate Fludrocortisone
26	80	128	95/60	100/72	43	Fludrocortisone
27	100	120	138/90	90/65	18	Nefazodone Fludrocortisone
28	66	107	130/80	120/93	40	none

BP = blood pressure; bpm = beats per minute; HR = heart rate; Iso = isoproterenol; max = maximum; μg/min = micrograms per minute.

and near syncope. Associated with these symptoms may be complaints of chronic fatigue or exercise intolerance, anxiety, cognitive impairment, and shortness of breath. Often, complaints such as these are passed off as being psychiatric in nature. However, our data suggests that these patients

have identifiable abnormal cardiovascular responses to the orthostatic stress imposed by passive head-up tilt, and often experience a marked reduction in symptoms following therapy directed at correcting this underlying autonomic imbalance.

In response to head-up tilt, these patients demonstrate an inappropriate tachycardia (≥ 30 beats/min increase within 10 minutes of upright tilt or a heart rate of ≥ 120 within 10 minutes of passive tilt) which may be but usually is not associated with mild hypotension during which symptoms are reproduced. In addition, many of these patients appear to exhibit exaggerated responses to isoproterenol infusion. We have never observed this pattern in normal subjects undergoing tilt table testing during 7 years' worth of experience in controls.[12]

These observations are not new, rather what is striking is how often nearly identical findings have been reported. In 1944, MacLean et al.[13] reported on a group of four patients with orthostatic tachycardia that was associated with only a mild fall in blood pressure and who complained of postural palpitations, lightheadedness, weakness, and exercise intolerance. They postulated that the mechanism of this response might be a defect in the venous blood return to the heart due to a disorder at the capillary-venous level. In 1966 Frohlich et al.[14] described two patients who manifested an orthostatic tachycardia of > 40 beats/min (without hypotension) who complained of extreme postural anxiety, lightheadedness, and near syncope. Both patients exhibited an exaggerated heart rate response to isoproterenol infusions and improved on β-blocker therapy. In 1982 Rosen and Cryer used the term Postural Tachycardia Syndrome to describe a patient with orthostatic tachycardia of > 44 beats/min without orthostatic hypotension, in a patient complaining of postural intolerance, palpitations, and fatigue.[15] Later, in 1986 Fouad et al. described a group of patients with orthostatic intolerance who exhibited orthostatic tachycardia and only mild hypotension, calling the condition "idiopathic hypovolemia."[16] Streeten et al.[17] reported on a group of 11 patients, with clinical characteristics virtually identical to our patients with orthostatic tachycardia without hypotension. By reinjecting sodium pertechnetate Tc 99 mm labeled erythrocytes and gamma counting over the calf regions in both supine and upright positions he was able to demonstrate excessive gravity-mediated venous pooling in the lower extremities. Streeten later published a second series of four similar patients who also showed a hypersensitivity to norepinephrine infusion.[18] Hoeldtke et al., in two reports, described a total of 13 patients with near syncope, fatigue, exercise intolerance, and cognitive impairment who manifested evident orthostatic tachycardia.[19,20] Schondorf et al.[5,10] and Low et al.[6] made a detailed analysis of patients (16 in total) who complained of disabling fatigue, exercise intolerance, bowel hypomotility, dizziness, and near syncope, who had been labeled as having an unexplained panic disorder or chronic anxiety. However, their cardiovascular responses to head-up tilt were markedly abnormal. The heart rate response to tilt varied from 120–170 beats/min and often attained these values by 2 minutes, with excessive oscillations during tilt. Although some patients developed modest reduction in blood pressure during tilt, most remained normotensive while a few had a prominent hypertensive response (in whom diastolic blood pressure rose by up to 50 mmHg, with large fluctuations). Schondorf and Low also first used the term POTS to describe this disorder and suggested that it may be an attenuated form of pandysautonomia. As with our patients, in half of their population a viral illness appeared to precede the onset of symptoms. Most recently, Khurana described a group of eight patients with virtually identical symptoms and tilt responses, who in addition appeared to have sudomotor abnormalities as well as other signs of mild autonomic dysfunction.[21]

Our findings confirm and expand upon these earlier observations. Taken together these data suggest that a group of patients exist with a mild form of autonomic dysfunction in which a deficiency in peripheral vascular function results in an excessive compensatory postural tachycardia, in addition to other signs of autonomic instability (such as constipation and sudomotor abnormalities). In addition, our data (along with that previously alluded to) suggest that these individuals can be readily identified by their cardiovascular responses during head upright tilt table testing. Indeed, Streeten has demonstrated that orthostatic tachycardia appears to be the most sensitive (and

earliest) index of mild orthostatic intolerance.[22] In addition, our data suggest that therapeutic measures aimed at altering autonomic balance may result in a lessening or resolution of what are often perceived as disabling symptoms in many (but not all) patients. Indeed, most of the patients who felt that their symptoms prevented them from working, following therapy were able to resume gainful employment.

POTS may often be misdiagnosed as either a psychiatric or anxiety related disorder (in a manner not dissimilar to the way patients with neurocardiogenic syncope were treated prior to the introduction of tilt table testing). Low et al., following extensive reviews of historical data, has postulated that POTS over the years may have masqueraded under such names as neurocirculatory asthenia, DaCosta syndrome, the effort syndrome, and soldier's heart syndrome.[6,10] Many patients with POTS could potentially be labeled as having chronic fatigue syndrome. Indeed, recent data from Rowe et al.[23] and Bou-Holiaigah et al.[24] on the results of tilt table testing in patients with chronic fatigue syndrome suggest that there may be considerable overlap between these two disorders.

Another fascinating aspect of both our data and those of Low et al.[6] and Schondorf and Low[5] is that a number of patient's reported that symptoms began following a viral infection of some sort, suggesting that in some individuals there may be an immune-mediated pathogenesis. In one of our patients symptoms began after an episode of sepsis and one after a motor vehicle accident. One patient stated that her symptoms began shortly after menopause. Interestingly, the vast majority of patients in our study were women (although that has not been the case in other studies). The reason for this may represent referral bias in that women may have been more likely to seek medical attention. There may also be physiological reasons for the greater number of women, as estrogen has been found to cause a reduction in peripheral vascular resistance, which in certain settings, such as the postpartum period, may be sufficiently profound so as to result in hypotension and syncope.[25] Low has reported that patients with migraines and sleep disorders may be overrepresented in the POTS population.[6] Of further interest is that six patients gave a history of extreme tachycardia, flushing, and near syncope after meal ingestion. Previously this phenomenon had only been reported in elderly patients. Jansen et al. have found that patients with these postprandial symptoms exhibit a failure to maintain systemic vascular resistance after eating, probably because of splanchic blood pooling without a compensatory increase in peripheral vascular resistance.[26]

It is difficult to make assessments of potential treatment options, as our selection of agents was based on our experiences treating neurocardiogenic syncope and more severe forms of autonomic dysfunction. However, we did find that fludrocortisone was often quite helpful in these individuals, either as mono or adjuvant therapy. In addition to the drugs' effects in increasing blood volume, fludrocortisone also appears to increase the sensitivity of blood vessels to the vasoconstrictive effects of endogenous norepinephrine.[26] Methylphenidate increases peripheral vascular resistance via alpha receptor stimulation.[27] β-blockers appeared helpful in patients who seemed hypersensitive to isoproterenol. The serotonin re-uptake inhibitors have been effective in both neurocardiogenic syncope and orthostatic hypotension, apparently via central nervous system actions.[28,29] Erythropoietin has been used in severe autonomic failure to raise and stabilize blood pressure.[8] Some investigators have reported that octreotide or ergot alkaloids may sometimes be effective.[19]

Thus, POTS is a recognizable and potentially treatable disorder in which patients demonstrate a marked orthostatic intolerance, manifested by postural tachycardia, palpitations, weakness and fatigue, exercise intolerance, dizziness, and near syncope. During baseline tilt table testing, these patients often exhihit an increase in heart rate of $>$ 30 beats/min in the first 10 minutes not associated with profound hypotension, or by a tachycardia of $>$ 120 beats/min within 10 minutes up-right not associated with profound hypotension or syncope. In either case the patients' symptoms should be reproduced. Patients may also exhibit an exaggerated response to low dose isoproterenol infusion. Treatments aimed at altering autonomic balance can often lessen the severity of symptoms.

Better recognition and diagnosis of this syndrome will not only allow for a better under-

standing of the nature of this disorder, but may also help this group of highly symptomatic patients return to their normal activities and gainful employment.

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