Hypertension
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Hyperadrenergic Postural Tachycardia Syndrome in Mast Cell Activation Disorders

Cyndya Shibao, Carmen Arzubiaga, L. Jackson Roberts II, Satish Raj, Bonnie Black, Paul Harris and Italo Biaggioni

Hypertension. 2005;45:385-390; originally published online February 14, 2005;
doi: 10.1161/01.HYP.0000158259.68614.40
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563

Hyperadrenergic Postural Tachycardia Syndrome in Mast Cell Activation Disorders

Cyndya Shibao, Carmen Arzubiaga, L. Jackson Roberts II, Satish Raj, Bonnie Black, Paul Harris, Italo Biaggioni

Abstract—Postural tachycardia syndrome (POTS) is a disabling condition that commonly affects otherwise normal young females. Because these patients can present with a flushing disorder, we hypothesized that mast cell activation (MCA) can contribute to its pathogenesis. Here we describe POTS patients with MCA (MCA+POTS), diagnosed by episodes of flushing and abnormal increases in urine methylhistamine, and compared them to POTS patients with episodic flushing but normal urine methylhistamine and to normal healthy age-matched female controls. MCA+POTS patients were characterized by episodes of flushing, shortness of breath, headache, lightheadedness, excessive diuresis, and gastrointestinal symptoms such as diarrhea, nausea, and vomiting. Triggering events include long-term standing, exercise, premenstrual cycle, meals, and sexual intercourse. In addition, patients were disabled by orthostatic intolerance and a characteristic hyperadrenergic response to posture, with orthostatic tachycardia (from 79±4 to 114±6 bpm), increased systolic blood pressure on standing (from 117±5 to 126±7 mm Hg versus no change in POTS controls), increased systolic blood pressure at the end of phase II of the Valsalva maneuver (157±12 versus 117±9 in normal controls and 119±7 mm Hg in POTS; $P=0.048$), and an exaggerated phase IV blood pressure overshoot (50±10 versus 17±3 mm Hg in normal controls; $P<0.05$). In conclusion, MCA should be considered in patients with POTS presenting with flushing. These patients often present with a typical hyperadrenergic response, but β-blockers should be used with great caution, if at all, and treatment directed against mast cell mediators may be required. (***Hypertension*. 2005; 45:385-390.**)

Key Words: autonomic nervous system ■ norepinephrine ■ tachycardia

Postural tachycardia syndrome (POTS) is a disabling condition that commonly affects otherwise normal young females. This disorder is characterized by symptoms of fatigue, tachycardia, shortness of breath, and even syncope on standing. The etiology is not clear, but 2 possibilities have been proposed previously. In the neuropathic variant, the primary defect is thought to be a partial autonomic denervation that compromises lower limbs with exaggerated orthostatic venous pooling,[1] and perhaps the kidneys with low levels of plasma renin activity.[2] Patients with the hyperadrenergic variant are thought to have centrally driven sympathetic activation.[3]

A circulating vasodilator could produce reflex sympathetic activation, presenting clinically as "hyperadrenergic" POTS. In our evaluation of patients with POTS, some described flushing episodes associated with orthostatic intolerance. On the basis of this observation, also reported by others,[4–6] we hypothesized that activated mast cells may provide a source of circulating vasodilators in a subset of patients with hyperadrenergic POTS. If true, histamine and other mast cell mediators could play an important role in the pathogenesis of this syndrome.

There is a wide spectrum of disorders associated with mast cell pathology. Mastocytosis is a common term used to define abnormal proliferation and accumulation of mast cells in 1 or more body tissues.[7] The clinical manifestation is produced by episodic release of mast cell mediators in response to specific stimuli[8] and can follow either an indolent or aggressive course ranging from circumscribed cutaneous involvement to life-threatening mast cell leukemia. In 1991, Roberts and Oates described the clinical syndrome of idiopathic mast cell activation (MCA).[9] In this condition, there is no evidence of mast cell proliferation, but patients are disabled by episodic MCA, documented by accumulation of mediators in plasma or urine. Patients with this syndrome typically present episodes or "attacks" of flushing accompanied by palpitations, lightheadedness, dizziness, shortness of breath, occasional nausea and diarrhea, headache, and syncope.

Here we describe patients disabled by persistent orthostatic intolerance and evidence of MCA. These patients often present with a typical hyperadrenergic variant of POTS and biochemical evidence of MCA. β-Blockers should be used with great caution in these patients, if at all, and treatment directed against mast cell mediators may be required.

Received August 9, 2004; first decision August 25, 2004; revision accepted December 20, 2004.

From the Division of Clinical Pharmacology, Department of Medicine and Pharmacology, and the Autonomic Dysfunction Center, Vanderbilt University School of Medicine, Nashville, Tenn.

Correspondence to Italo Biaggioni, MD, 1500 21st Ave S, Suite 3500, Clinical Trials Center, Vanderbilt University, Nashville, TN 37212. E-mail Italo.biaggioni@vanderbilt.edu

Hypertension is available at http://www.hypertensionaha.org

DOI: 10.1161/01.HYP.0000158259.68614.40

Methods

Subjects

We evaluated 177 subjects referred to the Vanderbilt Autonomic Dysfunction Clinic for disabling orthostatic intolerance who were studied as inpatients from January 1995 to January 2004. A patient was considered to have an MCA disorder and POTS (also known as orthostatic intolerance) if they met the following criteria. (1) Long-standing (>6 months) disabling orthostatic intolerance; (2) an increase in heart rate of ≥30 bpm within 5 minutes after assuming a standing position; (3) absence of an underlying cause (debilitating disease, substantial weight loss, prolonged bed rest, previous history of any disease producing peripheral neuropathy, or any medication impairing autonomic reflexes; (4) a history of facial or upper trunk flushing (defined as objective and intense facial redness witnessed by a physician or caregiver); and (5) urine methylhistamine >230 μg/g creatinine associated with a flushing episode.[9] Patients were classified into 3 separate groups. Eight young female subjects met the criteria of MCA and POTS (MCA+POTS). An additional 5 patients were identified as having similar characteristics, with the exception that they presented with orthostatic hypotension (OH; identified by a decrease in systolic blood pressure of >20 mm Hg or in diastolic blood pressure of >10 mm Hg; MCA+OH). We thought it important to include a group of 16 patients with a history of POTS with facial flushing but no evidence of MCA (documented by absence of increased urine methylhistamine, POTS). This provides a comparison group to determine whether the presence of MCA modifies the clinical presentation of POTS. We also include a fourth control group of 12 normal, healthy, age-matched females.

Procedures

All subjects were admitted to the Vanderbilt General Clinical Research Center and were fed a low-monoamine, caffeine-free diet containing 150 mEq sodium and 70 mEq potassium per day for at least 3 days before evaluation. Medications affecting the autonomic nervous system were withheld for at least 3 days before admission.

Autonomic function tests were used to evaluate the integrity of the different reflex arcs. These included Valsalva maneuver, the cold pressor and handgrip tests to assess cardiovascular autonomic function, and the sinus arrhythmia ratio (change in heart rate in response to controlled breathing) to assess cardiac parasympathetic activity.[10] All tests were standardized previously in our laboratory.[11] An orthostatic test was performed to evaluate hemodynamic and hormonal changes on standing. An indwelling catheter was placed in an antecubital vein to obtain blood samples while patients remained supine after an overnight rest. Subjects were encouraged to stand as long as possible or up to 30 minutes. During this period, they were allowed to sit at intervals if presyncopal symptoms developed. Blood samples were obtained for catecholamines, aldosterone, and renin measurements. Brachial blood pressure and heart rate were obtained using an automated sphygmomanometer (Dinamap; GE Medical Systems Information Technologies) during supine and standing test phases.

Plasma catecholamine levels were determined by high-performance liquid chromatography with electrochemical detection.[12] Plasma renin enzymatic activity was assessed by the conversion of angiotensinogen to angiotensin I and expressed as nanograms of angiotensin I produced per milliliter of plasma per hour. Plasma aldosterone was measured by radioimmunoassay.[13] Urine samples were obtained in patients with a history of flushing in the face or upper trunk. Patients were asked to collect urine for 4 hours immediately after a spontaneous severe flushing episode, defined by a subjective intensity of symptoms of "7 to 8" on a scale of "0" (no symptoms) to "10" (the worst symptoms ever). This was done during the inpatient or outpatient evaluation. Samples were obtained within 4 hours after a spontaneous episode. Methylhistamine levels were measured by gas chromatography negative ion chemical ionization mass spectrometry.[14] In no case was there any abnormality in hematologic laboratory results consistent with systemic mastocytosis.

To determine the response to treatment, a research nurse contacted the patients 3 months after discharge and obtained information about the medication, the frequency of mast cell episodes with flushing, and the intensity of orthostatic tachycardia. We were able to obtain information on 6 patients with MCA+POTS and in 3 patients with MCA+OH.

Statistical Analysis

Data were analyzed using SPSS version 11 (SPSS). Frequency tables were generated for categorical variables. Continuous variables are expressed as mean±SEM. Group comparisons were made using the nonparametric Kruskal–Wallis test. Post hoc analysis between 2 groups was made using the nonparametric Mann–Whitney test. Criterion for significance was $P<0.05$.

Results

Clinical Characteristics and Autonomic Response to Posture

Clinical characteristics of patients and controls are presented in Tables 1 and 2. All patients except 1 were female, and all were white, non-Hispanic, with an age range between 18 and 50 years. There was no significant difference in age, weight, and body mass index between groups. Symptoms during episodes included flushing, palpitations, lightheadedness with severe orthostatic intolerance, nausea, diarrhea, abdominal cramping, and polyuria. Blood pressure increased acutely in some cases. Patients often exhibited hypersomnia, sleeping for hours after these episodes.

Hemodynamic and humoral responses to posture are shown in Figures 1 and 2. As expected by the selection of subjects, standing heart rate was significantly higher in the MCA+POTS, POTS, and MCA+OH groups compared with normal subjects ($P<0.001$). Mean supine diastolic blood pressure was significantly different between groups ($P=0.005$); MCA+OH patients had higher values compared with MCA+POTS, POTS, and normal subjects. Upright systolic blood pressure was significantly increased in the MCA+POTS group compared with normal subjects (Table 1; Figure 2; $P=0.013$). We identified 5 patients who presented with orthostatic hypertension, defined by an increase in systolic blood pressure on standing of ≥20 mm Hg. Furthermore, 4 patients presented with episodes of sudden onset of hypertension and palpitations. There were no obvious triggering events, and these episodes resolved spontaneously. The supine and upright blood pressure obtained from these patients as well as the blood pressure values during the hypertensive crisis are presented in supplemental Table I and supplemental Figure Ia and Ib (available online at http://www.hypertensionaha.org).

Mean supine plasma norepinephrine levels were significantly different between groups: MCA+OH was higher than MCA+POTS, POTS, and normal subjects (Table 1; Figure 2; $P=0.004$). Supine plasma norepinephrine was also significantly higher in MCA+POTS patients compared with controls (269±41 and 129±22 pg/mL, respectively; $P<0.05$; Figure 2) but not compared with POTS patients. No differences were observed in supine and upright epinephrine, renin activity, or aldosterone.

As expected, the methylhistamine levels were different between patients with MCA+POTS and MCA+OH compared with POTS controls ($P<0.001$). Although not statistically significant, patients with MCA+OH tended to have higher levels of urinary methylhistamine compared with MCA+POTS patients (Table 1).

TABLE 1. Clinical Characteristics of Normal Controls, Patients With POTS, MCA+POTS, and MCA+OH

	Normal n=12	POTS n=16	MCA+POTS n=8	MCA+OH n=5	
Age (years)	31.5±1.4	32.1±2.8	38.0±2.9	34.4±4.7	NS
Weight (kg)	65.8±4.6	62.1±4.2	66.9±5.5	66.9±7.2	NS
BMI (kg/m^2)	24.1±1.6	22.3±1.4	25.7±2.1	23.3±1.4	NS
Heart rate (bpm)					
Supine	68±3	72±3	79±4	74±3	NS
Upright	86±3	111±4	114±6	114±8	<0.001*
Blood pressure (mm Hg)					
Systolic					
Supine	104±3	112±5	117±5	117±5	NS
Upright	107±3	112±5	126±7	95±6	0.021*
Diastolic					
Supine	62±2	65±2	70±3	82±3	0.005*
Upright	66±2	73±3	80±5	76±7	NS
Plasma norepinephrine (pg/mL)					
Supine	129±22	188±21	269±41	344±87	0.004*
Upright	405±40	676±60	745±83	673±67	0.003*
Plasma epinephrine (pg/mL)					
Supine	18±4	33±8	29±8	37±5	0.058
Upright	49±8	78±21	59±11	42±4	NS
Plasma renin activity (ng/mL/hour)					
Supine	1.0±0.3	1.0±0.2	0.9±0.3	1.0±0.2	NS
Upright	2.2±0.6	2.3±0.5	2.8±1.0	3.1±0.7	NS
Plasma Aldosterone (ng/mL/hour)					
Supine	11.9±3.1	12.7±4.0	7.2±1.4	10.4±2.8	NS
Upright	29.4±4.9	21.8±5.2	20.0±4.5	41.0±12.3	NS
†Methylhistamine (μg/g creatinine)	163.0±10.8	161.4±10.2	327.4±24.8	347.7±34.9	<0.001*

BMI indicates body mass index.

*P values were calculated by nonparametric test Kruskal–Wallis.

†Normal values range from 50–230 μg/g creatinine±2.5 DC of mean normal values.

Characterization of Autonomic Function

Autonomic function tests are presented in Table 3 and Figure 3. No significant differences in systolic blood pressure were observed between groups at baseline for Valsalva maneuver, the hyperventilation test, the cold pressor test, and the handgrip test. There was a difference in systolic blood pressure during phase II_{Late} of the Valsalva maneuver (P=0.048; Table 3; Figure 3). The MCA+POTS group had a significantly higher systolic blood pressure compared with POTS and normal controls (P=0.023 and P=0.027, respectively). During phase IV of the Valsalva maneuver, we observed that groups with MCA+POTS and POTS presented an excessive increase in systolic blood pressure (hypertensive overshoot) compared with normal controls (Figure 3). The change in systolic blood pressure between baseline and phase IV of the Valsalva maneuver was significantly higher in the MCA+POTS group (50±10 mm Hg) compared with the POTS group (31±5 mm Hg) and controls (17±3 mm Hg). In a post hoc analysis, no differences were found between patients with MCA+POTS and POTS (P=0.168). The systolic blood pressure and diastolic blood pressure after 1 minute of the cold pressor test and after 3 minutes of the handgrip test were different between groups. In MCA+POTS patients, systolic blood pressure increased 35±12 mm Hg during the cold pressor test, whereas the response in normal controls averaged 20±5 mm Hg.

Triggering of MCA With Exercise

Because patients often referred to episodes of flushing triggered by exercise, we performed treadmill exercise on 3 subjects. Flushing was triggered in these patients, and this was associated with an increased in urinary methylhistamine (supplemental Figure II). In 1 patient, we documented an increase in plasma histamine, indicative of mast cell degranulation but not of plasma prostaglandin D_2 (PGD_2), a marker of newly formed mast cell mediator release (supplemental Figure II).

Response to Treatment

The response to treatment in patients in whom follow-up was available is shown in supplemental Table II. Because of the

TABLE 2. Clinical Manifestation of Patients With POTS and MCA Disorder

	MCA+POTS		MCA+OH	
Orthostatic Symptoms—n (%)	n	%	n	%
Flushing	8	100	5	100
Palpitations	8	100	5	100
Lightheadedness	8	100	3	60
Chronic fatigue	7	88	3	60
Headache	5	63	2	40
Dizziness	5	63	4	80
Presyncope/syncope episodes	3	38	1	20
Shortness of breath	3	38	2	40
Confusion	3	38		
Increase in blood pressure	3	38		
Paresthesias	3	38		
Gastrointestinal symptoms (nausea and vomiting)	3	38	4	80
Abdominal cramps and diarrhea	3	38	3	60
Blurred vision	2	25		
Anxiety	2	25	1	20
Excessive diuresis			5	100
Orthostatic intolerance exacerbated by—n (%)				
After exercise	5	63	5	100
Prolonged standing	3	38	1	20
After meals	3	38	1	20
Premenstrual	2	25	1	20
Heat intolerance	2	25	5	100
Emotional stress	1	13	1	20
Sexual intercourse	1	13		

small number of patients, we did not attempt to perform a controlled study, and these observations remain anecdotal. However, it is noteworthy that patients improved clinically when treated with H_1 and H_2 histamine receptor blockers with the sympatholytic α-methyldopa, or with a combination of both. Of note, β-blockers triggered episodes consistent with acute MCA in 2 patients, and 4 patients had allergic reactions to aspirin, ranging from bronchoconstriction to anaphylaxis.

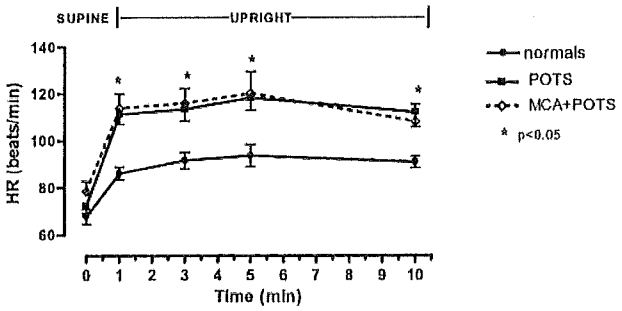

Figure 1. Dynamic change in heart rate (HR) induced by upright posture in normal subjects and patients with POTS and MCA+POTS. There was a significant difference in HR between both groups of patients and normal controls ($P<0.05$) already evident by the first minute of upright posture. There was no difference in HR response to posture between patient groups.

Discussion

We describe here a novel syndrome characterized by chronic disabling orthostatic tachycardia associated with episodes of systemic MCA. It affects otherwise normal young subjects, typically women, and causes substantial disability. We found no evidence of a primary diffuse autonomic neuropathy as the cause of this syndrome; autonomic reflexes appeared to be intact or overactive. On the contrary, exaggerated sympathetic activation was suggested by high plasma norepinephrine levels and increased systolic blood pressure in the upright posture. We and others have described patients with orthostatic intolerance, in many ways indistinguishable from patients presented here, who seem to have partial sympathetic denervation, preferentially involving lower limbs, the "neuropathic" POTS.[1] The clinical criteria that differentiate between the neuropathic and hyperadrenergic forms of this disease are not defined. We believe that the patients described in this report correspond to the hyperadrenergic form of POTS because of the exaggerated sympathetic pressor response during phase II_{Late} and phase IV of the Valsalva maneuver and the exaggerated increase in blood pressure on standing.

Episodes of MCA were documented in these patients by elevated levels of urinary methylhistamine taken immediately after a spontaneous event. It should be noted that urinary methylhistamine is usually normal in between episodes in patients with MCA disorders,[9] and patients should be instructed to collect urine for a 4-hour period immediately after a severe spontaneous flushing episode. Urinary histamine is often measured in the evaluation of flushing, but it is less specific than methylhistamine and not useful in the diagnosis of MCA. The symptoms described during these spells are probably induced by acute release of mast cell mediators such as histamine and PGD_2.[15,16] Patients with isolated MCA are symptomatic only during episodes, whereas our group of patients also experienced chronic fatigue and orthostatic intolerance in between episodes, eventually leading to a disabling condition.

Hypertension can be a prominent feature in some patients with MCA and POTS. We observed 2 different clinical presentations of this association. Patients may present with a consistent hypertensive response to upright posture or with acute hypertensive crisis. During these hypertensive episodes, blood pressure can increase to as high as 240/140 mm Hg, and the episodes are similar to the hypertensive variant of MCA disorders described previously.[9] These events resemble pheochromocytoma inasmuch as they are accompanied by tachycardia, nervousness, shortness of breath, and hypertension. A similar clinical presentation, known as pseudopheochromocytoma or diencephalic hypertension, has been described by Page.[17] Flushing is prominent in MCA disorders and in pseudopheochromocytoma and is a useful clinical distinction with pheochromocytoma, which is accompanied by pallor. Plasma norepinephrine is increased in both conditions, but levels are much higher in pheochromocytoma because catecholamines are released directly into the circulation, whereas in pseudopheochromocytoma, catecholamines are released into the synapse, and only a relatively small proportion spills over into the circulation.

We also report a group of patients with flushing and orthostatic intolerance but no evidence of MCA. The cause of flushing in those patients is not clear. Other entities associated with flushing and similar clinical characteristics are associated with dopamine release,

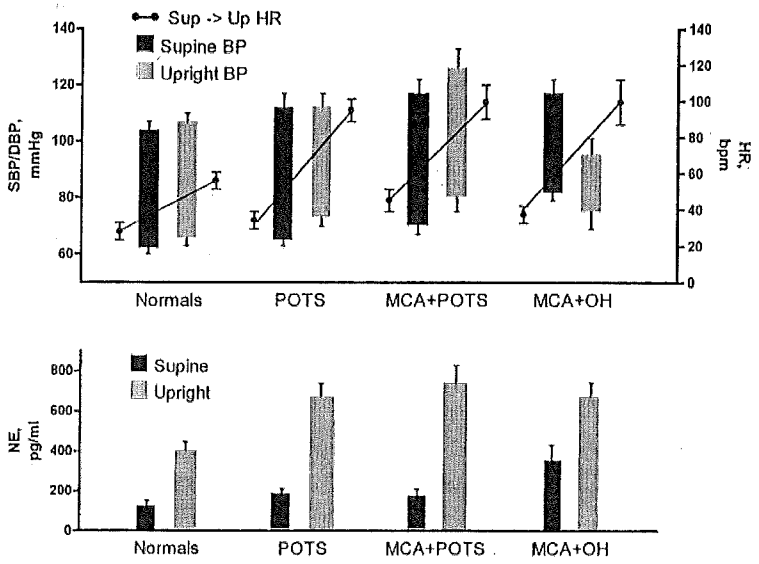

Figure 2. Hemodynamic and humoral effect of posture in normal subjects and patients with POTS, MCA+POTS, and MCA+OH. Top, Postural change in heart rate (HR; ●) and systolic/diastolic blood pressure (floating bars). Bottom, Supine and upright plasma norepinephrine (NE) taken from an antecubital vein. For statistically significant differences, see Table 1.

as described by Kuchel.[18] Panic attacks can also be associated with flushing and regional sympathetic activation,[19] but patients usually do not experience orthostatic intolerance between attacks.

Mast cells are localized in close proximity to blood vessels and peripheral nerves and are therefore strategically positioned to modulate sympathetic activity, vascular tone, and angiogenesis.[20] Histamine is a powerful vasodilator that could explain the cutaneous vasodilatation responsible for flushing. With regard to the pathophysiology underlying the association between POTS and MCA, we propose a positive feedback loop by which MCA, with the subsequent release of vasoactive mediators, may contribute to vasodilation, reflex sympathetic activation, central volume contraction, norepinephrine release, and orthostatic intolerance (Figure 4).

TABLE 3. Results of Autonomic Function Tests in Normal Controls, and in Patients With POTS and MCA+POTS

	Normal n=12	POTS n=16	MCA+POTS n=8	
	Mean SEM	Mean SEM	Mean SEM	*P* Value
Autonomic function test				
S/A ratio	1.4±0.1	1.4±0.1	1.3±0.1	NS
Valsalva maneuver				
Baseline SBP (mm Hg)	118±4	129±5	133±7	NS
Baseline DBP (mm Hg)	67±3	69±3	70±3	NS
SBP phase IIe (mm Hg)	97±6	104±6	112±5	NS
DBP phase IIe (mm Hg)	62±4	69±4	72±3	NS
SBP phase IIL (mm Hg)	117±9	119±7	157±12	0.048
DBP phase IIL (mm Hg)	78±6	72±6	96±8	NS
SBP phase IV (mm Hg)	135±5	160±6	184±13	0.005
DBP phase IV (mm Hg)	78±3	88±4	92±5	NS
Valsalva ratio	1.6±0.1	1.7±0.1	1.8±0.1	NS
Cold pressor test				
Baseline SBP (mm Hg)	108±3	116±5	122±5	NS
Baseline DBP (mm Hg)	64±3	72±3	71±4	NS
1 min SBP (mm Hg)	128±7	142±5	157±14	0.049
1 min DBP (mm Hg)	79±4	91±4	98±7	0.050
Handgrip				
Baseline SBP (mm Hg)	109±3	114±4	117±5	NS
Baseline DBP (mm Hg)	63±2	67±3	74±2	0.040
3 min SBP (mm Hg)	119±3	132±6	137±4	0.020
3 min DBP (mm Hg)	70±3	86±4	87±5	0.009

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; S/A, sinus arrhythmia.

P values were calculated by the Kruskal–Wallis test.

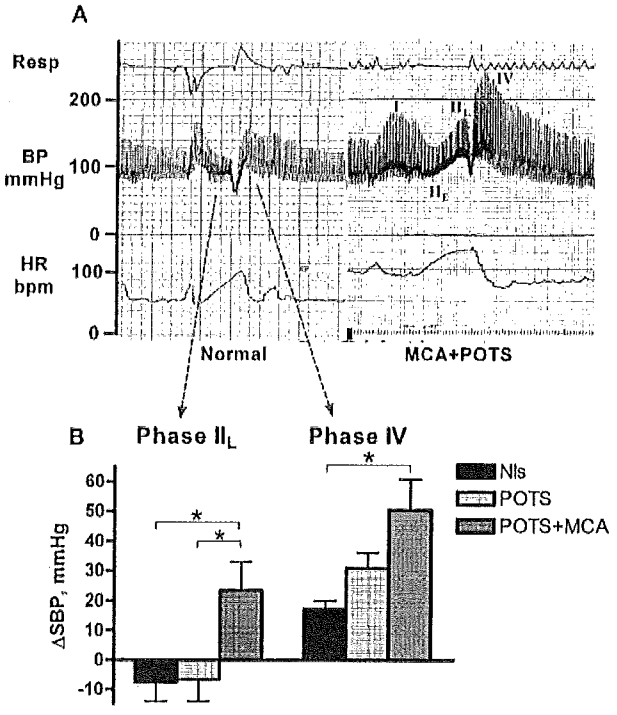

Figure 3. Cardiovascular response to the Valsalva maneuver in normal controls (Nls), patients with POTS, and patients with MCA+POTS. A, Comparison of representative tracings of a normal control and a patient with MCA+POTS showing the exaggerated increase in blood pressure during phase II_{Late} and phase IV. Resp indicates respirations; BP, blood pressure; HR, heart rate. B, Mean change in systolic blood pressure (ΔSBP) during late phase II (II_L) and phase IV of the Valsalva maneuver.

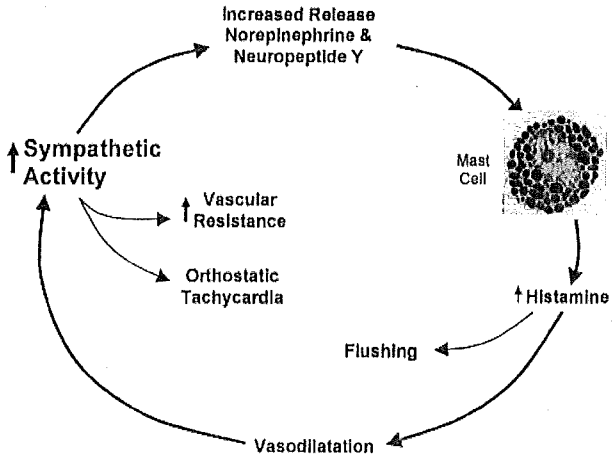

Figure 4. Proposed pathophysiological mechanisms underlying the association between MCA and hyperadrenergic orthostatic intolerance. See Discussion.

Conversely, our results indicate that exercise can lead to MCA, presumably through sympathetic activation. In this regard, neuropeptide Y (NPY), a 36-aa neuropeptide that is coreleased with norepinephrine from noradrenergic neurons, has been shown to induce mast cell degranulation with the release of preformed mediators in purified rat peritoneal[21,22] and human jejunal mast cells[23] and to induce hypotension in animals secondary to MCA in vivo.[24] This appears to be a nonreceptor-mediated effect related to the presence of positively charged amino acid residues of the C terminus of NPY. Therefore, the physiological significance of NPY-mediated MCA remains speculative.

Our findings have potential implications for the treatment of these patients. Because of the prominent orthostatic tachycardia, β-blockers are commonly used in the treatment of POTS patients. However, these drugs should be used with great caution in these patients, if at all, because of possible worsening of MCA. In our experience, a therapeutic trial with α-methyldopa should be considered, given the evidence of a hyperadrenergic state. Some patients may require treatment directed at controlling mast cell mediators, including H_1 and H_2 receptor antagonists.

Perspectives

We report a novel syndrome of chronic hyperadrenergic orthostatic intolerance associated with episodes of MCA. This syndrome should be considered in POTS patients with a history of flushing. This symptom is often not volunteered by patients and may require careful questioning by the physician. Diagnosis requires biochemical documentation of MCA because other causes of flushing can be associated with POTS. A correct diagnosis is important because the presence of MCA mandates a different approach in the treatment of these patients. β-Blockers, a commonly used therapeutic option in POTS patients, should be used with caution, if at all, because of the risk of triggering MCA. These patients can be treated with H_1/H_2 histamine antagonist and central sympatholytics.

Acknowledgments

This research was supported in part by a general clinical research center grant from National Center for Research Resources and by grants HL56693 and HL67232 from the National Institutes of Health. S.R.R. is supported by a K12 grant from the National Institutes of Health. C.S. is recipient of the international fellowship in clinical pharmacology supported by Merck Foundation.

References

1. Jacob G, Costa F, Shannon JR, Robertson RM, Wathen M, Stein M, Biaggioni I, Ertl A, Black B, Robertson D. The neuropathic postural tachycardia syndrome. *N Engl J Med.* 2000;343:1008–1014.
2. Jacob G, Robertson D, Mosqueda-Garcia R, Ertl AC, Robertson RM, Biaggioni I. Hypovolemia in syncope and orthostatic intolerance role of the renin-angiotensin system. *Am J Med.* 1997;103:128–133.
3. Jordan J, Shannon JR, Diedrich A, Black BK, Robertson D. Increased sympathetic activation in idiopathic orthostatic intolerance: role of systemic adrenoreceptor sensitivity. *Hypertension.* 2002;39:173–178.
4. Kuchel O, Leveille J. Idiopathic hypovolemia: a self-perpetuating autonomic dysfunction? *Clin Auton Res.* 1998;8:341–346.
5. Biaggioni I. Orthostatic intolerance syndrome, vasoregulatory asthenia and other hyperadrenergic states. In: Robertson D, Biaggioni I, eds. *Disorders of the Autonomic Nervous System.* London, UK: Harwood Academic Publishers; 1995.
6. Streeten DH, Kerr CB, Kerr LP, Prior JC, Dalakos TG. Hyperbradykininism: a new orthostatic syndrome. *Lancet.* 1972;2:1048–1053.
7. Valent P, Akin C, Sperr WR, Horny HP, Metcalfe DD. Mast cell proliferative disorders: current view on variants recognized by the World Health Organization. *Hematol Oncol Clin North Am.* 2003;17:1227–1241.
8. Castells M, Austen KF. Mastocytosis: mediator-related signs and symptoms. *Int Arch Allergy Immunol.* 2002;127:147–152.
9. Roberts LJ, Oates JA. Biochemical diagnosis of systemic mast cell disorders. *J Invest Dermatol.* 1991;96:19S–24S.
10. Mosqueda-Garcia R. Evaluation of the autonomic nervous system. In: Robertson D, Biaggioni I, eds. *Disorders of the Autonomic Nervous System.* London, UK: Harwood Academic Publishers; 1995.
11. Robertson D. Clinical pharmacology: assessment of autonomic function. In: *Clinical Diagnostic Manual for the House Officer.* Baltimore, Md: William and Wilkins; 1981.
12. Goldstein DS, Eisenhofer G, Stull R, Folio CJ, Keiser HR, Kopin IJ. Plasma dihydroxyphenylglycol and the intraneuronal disposition of norepinephrine in humans. *J Clin Invest.* 1988;81:213–220.
13. Workman RJ, Sussman CR, Burkitt DW, Liddle GW. Circulating levels of angiotensin I measured by radioimmunoassay in hypertensive subjects. *J Lab Clin Med.* 1979;93:847–856.
14. Roberts LJ, Oates JA. Accurate and efficient method for quantification of urinary histamine by gas chromatography negative ion chemical ionization mass spectrometry. *Anal Biochem.* 1984;136:258–263.
15. Morrow JD, Guzzo C, Lazarus G, Oates JA, Roberts LJ. Improved diagnosis of mastocytosis by measurement of the major urinary metabolite of prostaglandin D2. *J Invest Dermatol.* 1995;104:937–940.
16. Roberts LJ, Sweetman BJ, Lewis RA, Austen KF, Oates JA. Increased production of prostaglandin D2 in patients with systemic mastocytosis. *N Engl J Med.* 1980;303:1400–1404.
17. Page IH. A syndrome simulating diencephalic stimulation occurring in patients with essential hypertension. *Am J Med Sci.* 1935;190:9–14.
18. Kuchel O, Buu NT, Hamet P, Larochelle P, Gutkowska J, Schiffrin EL, Bourque M, Genest J. Orthostatic hypotension: a posture-induced hyperdopaminergic state. *Am J Med Sci.* 1985;289:3–11.
19. Wilkinson DJ, Thompson JM, Lambert GW, Jennings GL, Schwarz RG, Jefferys D, Turner AG, Esler MD. Sympathetic activity in patients with panic disorder at rest, under laboratory mental stress, and during panic attacks. *Arch Gen Psychiatry.* 1998;55:511–520.
20. Feoktistov I, Ryzhov S, Goldstein AE, Biaggioni I. Mast cell-mediated stimulation of angiogenesis: cooperative interaction between A2B and A3 adenosine receptors. *Circ Res.* 2003;92:485–492.
21. Arzubiaga C, Morrow J, Roberts LJ, Biaggioni I. Neuropeptide Y, a putative cotransmitter in noradrenergic neurons, induces mast cell degranulation but not prostaglandin D2 release. *J Allergy Clin Immunol.* 1991;87:88–93.
22. Grundemar L, Hakanson R. Neuropeptide Y, peptide YY and C-terminal fragments release histamine from rat peritoneal mast cells. *Br J Pharmacol.* 1991;104:776–778.
23. Santos J, Saperas E, Nogueiras C, Mourelle M, Antolin M, Cadahia A, Malagelada JR. Release of mast cell mediators into the jejunum by cold pain stress in humans. *Gastroenterology.* 1998;114:640–648.
24. Shen GH, Grundemar L, Zukowska-Grojec Z, Hakanson R, Wahlestedt C. C-terminal neuropeptide Y fragments are mast cell-dependent vasodepressor agents. *Eur J Pharmacol.* 1991;204:249–256.

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2011, Vol. 18, No. X, pp. 1–x

ISSN 1897–5593

Clinical presentation and management of patients with hyperadrenergic postural orthostatic tachycardia syndrome. A single center experience

Khalil Kanjwal[1], Bilal Saeed[2], Beverly Karabin[1], Yousuf Kanjwal[1], Blair P. Grubb[1]

[1]Section of Electrophysiology, Division of Cardiology, Department of Medicine, University of Toledo Medical Center, Toledo, OH, USA
[2]Division of Internal Medicine, Department of Medicine, University of Toledo Medical Center, Toledo, OH, USA

Abstract

Background: *We present our single center experience of 27 patients of hyperadrenergic postural orthostatic tachycardia syndrome (POTS).*

Methods: *In a retrospective analysis, we reviewed the charts of 300 POTS patients being followed at our autonomic center from 2003 to 2010, and found 27 patients eligible for inclusion in this study. POTS was defined as symptoms of orthostatic intolerance (of greater than six months' duration) accompanied by a heart rate increase of at least 30 bpm (or a rate that exceeds 120 bpm) that occurs in the first 10 min of upright posture or head up tilt test (HUTT) occurring in the absence of other chronic debilitating disorders. Patients were diagnosed as having the hyperadrenergic form based on an increase in their systolic blood pressure of ≥ 10 mm Hg during the HUTT (2) with concomitant tachycardia or their serum catecholamine levels (serum norepinephnrine level ≥ 600 pg/mL) upon standing.*

Results: *Twenty seven patients, aged 39 ± 11 years, 24, (89%) of them female and 22 (82%) Caucasian were included in this study. Most of these patients were refractory to most of the first and second line treatments, and all were on multiple combinations of medications.*

Conclusions: *Hyperadrenergic POTS should be identified and differentiated from neuropathic POTS. These patients are usually difficult to treat and there are no standardized treatment protocols known at this time for patients with hyperadrenergic POTS.* (Cardiol J 2011; 18, x: xx–xx)

Key words: postural tachycardia syndrome, hyperadrenergic, orthostatic intolerance

Introduction

Postural orthostatic tachycardia syndrome (POTS) is characterized by symptoms of orthostatic intolerance upon assuming an upright posture and relief of these symptoms by recumbency [1, 2]. The current definition of POTS is the presence of symptoms of orthostatic intolerance (> 6 months duration) associated with a heart rate (HR) increase of 30 bpm (or rate that exceeds 120 bpm) that occurs within the first 10 min of standing or upright tilt, not associated with other chronic debilitating conditions

Address for correspondence: Prof. Blair P. Grubb, MD, FACC, Director Electrophysiology Services, Division of Cardiology, Department of Medicine, Health Sciences Campus, The University of Toledo Medical Center, Mail Stop 1118, 3000 Arlington Ave, Toledo, OH 43614, USA, tel: 419 383 3778, fax: 419 383 3041, e-mail: blair.grubb@utoledo.edu

Received: 14.04.2011 Accepted: 20.06.2011

such as prolonged bed rest or the use of medications known to diminish vascular or autonomic tone [1, 2].

In recent years there has been a substantial improvement of our understanding of POTS. Although the exact etiology remains elusive, we know that the syndrome of postural tachycardia is not a single clinical entity, but rather a heterogeneous group of various related clinical syndromes having a final common presentation of orthostatic intolerance.

The commonest form of POTS, called the neuropathic or partial dysautonomic form, results from neuropathy preferentially involving the lower extremities with resultant venous pooling [3–6]. Another group of patients suffer from centrally driven abnormal sympathetic activation. This form of postural tachycardia syndrome is called hyperadrenergic POTS, and comprises about 10% of all POTS patients. Patients suffering from hyperadrenergic POTS have been observed to have an orthostatic plasma norepinephrine level ≥ 600 pg/mL and a rise of systolic blood pressure (SBP) of ≥ 10 mm Hg upon standing [1, 2, 6–8]. We present our single center experience of 27 hyperadrenergic POTS patients.

Methods

This was a retrospective study approved by our local Institutional Review Board. We reviewed charts of 300 POTS patients seen at our autonomic center between 2003 and 2010 and found 27 patients eligible for inclusion in this study.

Criterion for diagnosis of POTS

Postural orthostatic tachycardia was defined as symptoms of orthostatic intolerance (of greater than six months' duration) accompanied by a HR increase of at least 30 bpm (or a rate that exceeds 120 bpm) observed during the first 10 min of upright posture or head up tilt test (HUTT) occurring in the absence of other chronic debilitating disorders [1, 2]. Symptoms include fatigue, orthostatic palpitations, exercise intolerance, light-headedness, diminished concentration, headache, near-syncope and syncope. In a retrospective chart review, we collected data including demographic information, presenting symptoms, laboratory data, tilt-table response, and treatment outcomes.

Criterion for diagnosis of hyperadrenergic postural tachycardia syndrome

Patients were diagnosed as having the hyperadrenergic form based on an increase in their SBP of ≥ 10 mm Hg during the HUTT [2] with concomitant tachycardia or their serum catecholamine levels (serum norepinephnrine level ≥ 600 pg/mL) upon standing [1, 2]. Each patient had been evaluated for the presence of a pheochromocytoma by a computed tomography scan of the abdomen, as well as metaiodobenzylguanidine scanning. In no patient was a pheochromocytoma detected.

HUTT protocol

The protocol used for tilt table testing has been described elsewhere [1, 7, 9–12], but basically consisted of a 70-degree baseline upright tilt for a period of 30 min, during which time HR and blood pressure were monitored continually. If no symptoms occurred, the patient was lowered to the supine position and an intravenous infusion of isoproterenol started, with a dose sufficient to raise the HR to 20–25% above the resting value. Upright tilt was then repeated for 15 min. Patients were included in the study if they had a POTS pattern on HUTT (rise in HR without any change in blood pressure).

Treatment protocols

The treatment protocols employed were based on our previous experiences with orthostatic disorders and are described in detail elsewhere [1, 7, 9–12]. Briefly, a sequence of therapies was employed that included physical counter maneuvers and aerobic and resistance training, as well as increased dietary fluids and sodium. If these were ineffective, pharmacotherapy was initiated in a sequence generally consisting of beta-blockers, central sympatholytics, fludrocortisone, midodrine, and selective serotonin reuptake inhibitors, either alone or in combination. As this was a retrospective chart review, a formal questionnaire to assess the response to treatment or an assessment of response to treatment by HUTT testing was not employed. Information about the subjective symptoms and sense of well-being from each patient was collected from the patient's charts, physician communications and direct patient inquiry. A treatment was considered successful if it provided symptomatic relief.

Statistical analysis

Statistical analysis was done using SPSS15. The data is observational and is presented as mean ± ± SD and percentages.

Results

Table 1 summarizes the clinical features, comorbid conditions, precipitating events and symp-

Table 1. Clinical features of patients with hyperadrenergic postural orthostatic tachycardia.

Age (years)	39 ± 11
Sex (female)	24 (88.9%)
Race (Caucasian)	22 (81.5%)
Co-morbidity:	
Hypertension	9 (33.3%)
Diabetes mellitus	2 (7.4%)
Coronary artery disease	2 (7.4%)
Migraine	8 (29.6%)
Joint hypermobility syndrome	5 (18.5%)
Mitochondrial cytopathy	1 (3.7%)
Precipitating event:	
Trauma	1 (3.7%)
Pregnancy	3 (12.5%)
Viral infection	3 (11.1%)
Symptoms:	
Fatigue	14 (51.9%)
Orthostatic palpitation	13 (48.2%)
Orthostatic hypertension	5 (18.5%)
Dizziness/pre-syncope	16 (59.3%)
Syncope	11 (40.7%)
Anxiety	18 (67%)
Tremulousness	18 (67%)
Excessive sweating	14 (52%)
Nausea	9 (33%)
Diarrhea	10 (35%)
Bloating	9 (33%)

toms of patients suffering from hyperadrenergic POTS. Twenty seven patients aged 39 ± 11, 24 (89%) of them female and 22 (82%) of them Caucasian were included in this study.

Precipitating events

The precipitating events in patients suffering from hyperadrenergic POTS were pregnancy (12.5%), viral infection (11.1%) and trauma (1%).

Comorbidity

Hypertension (33.3%), migraine (29.6%) and joint hypermobility syndrome (18.5%) were common co-morbidities in this group of patients.

Symptoms of POTS

Dizziness and pre-syncope (60%) were the common symptoms, followed by fatigue (51%) and orthostatic palpitations (48%). Orthostatic hypertension was seen in 19% of patients. Table 1 summarizes other symptoms encountered in our patient population.

Table 2. Medication use and response to different medications used in patients with hyperadrenergic postural orthostatic tachycardia.

Medication	Used in patients	Response to medication
Adderall	4/27 (14.8%)	4/4 (100%)
Florinef	4/27 (14.8%)	1/4 (25%)
Clonidine	12/27 (44.4%)	10/12 (83.3%)
Beta-blockers	24/27 (88.9%)	13/20 (65.0%)
Midodrine	9/27 (33.3%)	4/7 (57.1%)
SSRI	9/27 (33.3%)	3/7 (42.9%)
SSRI/NERI	17/27 (62.9%)	7/13 (53.9%)
Modafinil	5/27 (18.5%)	3/5 (60.0%)
Epogen	2/27 (7.4%)	1/2 (50.0%)
Mestinon	11/27 (40.7%)	2/8 (25.0%)

SSRI — selective serotonin reuptake inhibitors; NERI — norepinephrine reuptake inhibitors

Tilt table test

All patients demonstrated a typical hyperadrenergic POTS response to the tilt table test. The mean rise in HR on a tilt test was 35 ± 3 bpm and the mean time to peak HR was 8 ± 3 min. The mean increase in SBP was 13 ± 3 mm Hg.

Norephinephrine levels

The standing norepinephrine levels were calculated in each patient. The mean norepinephrine levels in these patients were 828 ± 200 pg/mL (normal range: 520 pg/mL).

Medications and response to the medications

Most of these patients were on a combination of medications. The algorithm we used has been described in the 'Methods' section under 'Treatment protocol'. Most of these patients were receiving a combination of various first and second line medications. These patients were refractory to various combinations of medications. Table 2 summarizes various medications we commonly used in these patients.

Discussion

Our understanding of the disorder now called POTS has substantially increased over the past two decades. The early descriptions of the disorder focused on a group of patients who had been previously healthy until a sudden febrile illness (presumably viral) brought on an abrupt onset of symptoms [3].

Later investigations revealed that POTS is better understood as a physiological state most commonly due to an inability of the peripheral vasculature to maintain adequate resistance in the face of orthostatic stress, allowing for excessive pooling of blood in the more dependent areas of the body [1, 13, 14]. The resultant functional decline in circulatory volume elicits a compensatory increase in HR and myocardial contractility. While compensatory in mild cases, this mechanism is unable to fully compensate in more severe cases, resulting in a reduction in effective circulation and varying degrees of cerebral hypoperfusion. Later investigations revealed that POTS is not a single condition, but rather a heterogeneous group of disorders resulting in a similar physiological state [8, 13–15].

Clinical findings of hyperadrenergic POTS in our series

Precipitating events. The less common form of primary POTS, the hyperadrenergic form, tends to have a gradual and progressive onset of symptoms as opposed to an abrupt onset [2, 16]. In our study, one patient had onset years after traumatic brain injury, three had symptoms following pregnancy, and another three had an onset of symptoms following a viral illness.

Symptoms of POTS. Hyperadrenergic POTS patients report significant tremor, anxiety, and cold sweaty extremities when upright. Many will report a significant increase in urinary output after being upright for even a short period of time, and over half suffer from true migraine headaches. In our series, 55–65% of patients reported symptoms of hyperadrenergic state in the form of anxiety, tremulousness and excessive sweating. Orthostatic palpitations and pre-syncope/dizziness were reported in 50–60% of the patients. Fatigue was one of the commonest symptoms reported in our patient series and syncope was also reported in 40%. Some patients with POTS may experience syncope in the absence of significant decline in blood pressure. A sudden increase in cerebrovascular resistance resulting in decline in cerebral oxygenation that occurs in the presence of orthostatic stress has also been reported in these patients [17–20]. The higher incidence of syncope and fatigue may be because of the selection bias in this study as many of these patients had been referred from various centers for a second opinion regarding diagnosis and management and were often difficult to treat with refractory symptoms.

Gastrointestinal symptoms were reported in almost 30% of the patients in this study. There have been reports of gastrointestinal symptoms in patients suffering from POTS. Patients with hyperadrenergic forms tend to diarrhea rather than constipation [2, 7]. In our series, almost 30% of patients had gastrointestinal symptoms in form of nausea, bloating and diarrhea.

In our study, most patients demonstrated symptoms of adrenergic overactivity in the form of palpitations, tremulousness and almost one third of our patients were hypertensive, receiving more than two medications to control their blood pressure. Almost 20% of our patients demonstrated orthostatic rise in their blood pressure of more than 20 mm Hg. In some ways the symptoms patients experience are suggestive of pheochromocytoma, although no patient had evidence of this.

The patients suffering from hyperadrenergic variant of POTS appear to have an increased centrally mediated drive of norepinephrine or a defect in norepinephrine reuptake, resulting in increased availability of norepinephrine at the synaptic junctions. Beta-blockers and centrally acting sympatholytics like clonidine, by counteracting the excess norepinephrine either by decreasing the centrally mediated release or by receptor blockage, may result in a substantial decline in norepinephrine mediated effects [1, 2, 8, 15, 16].

Future perspective

There has been a substantial increase in the efforts to understand the pathophysiology and etiology of POTS. Recent research has shown that this syndrome may have multiple etiologies, and we now know that POTS can have multiple variants resulting from these multiple etiologies including partial dysautonomia [3] centrally mediated hyperadrenergic stimulation [8], norepinephrine transporter dysfunction [16], autoimmune anti body against cholinesterase receptors [21], POTS associated with deconditioning [22] and hypovolumia [23]. A recently published study reported that POTS may be a manifestation of autonomic cardiac neuropathy [24]. POTS has been reported after traumata [25] and infections [26] as well.

The clinical profile of our patients was similar to the patients reported in other studies. Also our observations that beta-blockers and centrally acting sympatholytics work better in patients presumed to have hyperadrenergic variant of POTS were consistent with those in other series [2, 7].

Conclusions

Patients of hyperadrenergic POTS should be identified and differentiated from those with neu-

ropathic POTS. These patients are usually difficult to treat and there are no standardized treatment protocols known at this time for patients with hyperadrenergic POTS. A randomized control trail in future may help evaluate the role of optimal therapy in these patients.

Acknowledgements

The authors do not report any conflict of interest regarding this work.

References

1. Grubb BP, Kanjwal Y, Kosinski DJ. The postural tachycardia syndrome. A concise guide to diagnosis and management. J Cardiovasc Electrophysiol, 2006; 17: 108–112.
2. Low PA, Sandroni P, Joyner M, Shen WK. Postural tachycardia syndrome (POTS). J Cardiovasc Electrophysiol, 2009; 20: 352–358.
3. Jacob G, Costa F, Shannon JR et al. The neuropathic postural tachycardia syndrome. N Engl J Med, 2000; 343: 1008–1014.
4. Low PA, Opfer-Gehrking TL, Textor SC et al. Comparison of the postural tachycardia syndrome (POTS) with orthostatic hypotension due to autonomic failure. J Auton Nerv Syst, 1994; 50: 181–188.
5. Schondorf R, Low PA. Idiopathic postural orthostatic tachycardia syndrome: An attenuated form of acute pandysautonomia? Neurology, 1993; 43: 132–137.
6. Garland EM, Raj SR, Black BK, Harris PA, Robertson D. The hemodynamic and neurohumoral phenotype of postural tachycardia syndrome. Neurology, 2007; 69: 790–798.
7. Thieben M, Sandroni P, Sletten D et al. Postural orthostatic tachycardia syndrome — Mayo Clinic experience. Mayo Clin Proc, 2007; 82: 308–313.
8. Jordan J, Shannon JR, Diedrich A, Black BK, Robertson D. Increased sympathetic activation in idiopathic orthostatic intolerance: Role of systemic adrenoreceptor sensitivity. Hypertension, 2002; 39: 173–178.
9. Kanjwal Y, Kosinski D, Grubb BP. The postural orthostatic tachycardia syndrome: Definitions, diagnosis, and management. Pacing Clin Electrophysiol, 2003; 26: 1747–1757.
10. Grubb BP. Postural tachycardia syndrome. Circulation, 2008; 117: 2814–2817.
11. Grubb BP, Kosinski DJ, Kanjwal Y. Orthostatic hypotension: Causes, classification, and treatment. Pacing Clin Electrophysiol, 2003; 26 (4 Part 1): 892–901.
12. Grubb BP, Kanjwal MY, Kosinski DJ. The postural orthostatic tachycardia syndrome: Current concepts in pathophysiology diagnosis and management. J Interv Card Electrophysiol, 2001; 5: 9–16.
13. Rowe PC, Barron DF, Calkins H, Maumenee IH, Tong PY, Geraghty MT. Orthostatic intolerance and chronic fatigue syndrome associated with Ehlers-Danlos syndrome. J Pediatr, 1999; 135: 494–499.
14. Gazit Y, Nahir M, Grahame R, Jacob G. Dysautonomia in the joint hypermobility syndrome. Am J Med, 2003; 115: 33–40.
15. Shibao C, Arzubiaga C, Roberts LJ et al. Hyperadrenergic postural tachycardia syndrome in mast cell activation disorders. Hypertension, 2005; 45: 385–390.
16. Shannon JR, Flattem NL, Jordan J et al. Orthostatic intolerance and tachycardia associated with norepinephrine-transporter deficiency. N Engl J Med, 2000; 342: 541–549.
17. Jordan J, Shannon JR, Black BK et al. Raised cerebrovascular resistance in idiopathic orthostatic intolerance: Evidence for sympathetic vasoconstriction. Hypertension,1998; 32: 699–704.
18. Grubb BP, Samoil D, Kosinski D et al. Cerebral syncope: Loss of consciousness associated with cerebral vasoconstriction in the absence of systemic hypotension. Pacing Clin Electrophysiol, 1998; 21: 652–658.
19. Ocon AJ, Medow MS, Taneja I, Clarke D, Stewart JM. Decreased upright cerebral blood flow and cerebral autoregulation in normocapnic postural tachycardia syndrome. Am J Physiol Heart Circ Physiol, 2009; 297: H664–H673.
20. Rodríguez-Núñez A, Fernandez Cebrián S, Perez-Muñuzuri A, Martinón-Torres F, Eirís-Puñal J, Martinón-Sánchez JM. Cerebral syncope in children. J Pediatr, 2000; 136: 542–544.
21. Vernino S, Low PA, Fealey RD, Stewart JD, Farrugia G, Lennon VA. Autoantibodies to ganglionic acetylcholine receptors in autoimmune autonomic neuropathies. N Engl J Med, 2000; 343: 847–855.
22. Levine BD, Zuckerman JH, Pawelczyk JA. Cardiac atrophy after bed-rest deconditioning: A nonneural mechanism for orthostatic intolerance. Circulation, 1997; 96: 517–525.
23. Raj SR, Robertson D. Blood volume perturbations in the postural tachycardia syndrome. Am J Med Sci, 2007; 334: 57–60.
24. Haensch CA, Lerch H, Schlemmer H, Jigalin A, Isenmann S. Cardiac neurotransmission imaging with 123I-meta-iodobenzylguanidine in postural tachycardia syndrome. J Neurol Neurosurg Psychiatry, 2010; 81: 339–343.
25. Kanjwal K, Karabin B, Kanjwal Y, Grubb BP. Autonomic dysfunction presenting as postural tachycardia syndrome following traumatic brain injury. Cardiol J, 2010; 17: 482–487.
26. Kanjwal K, Karabin B, Kanjwal Y, Grubb BP. Postural orthostatic tachycardia syndrome following Lyme disease. Cardiol J, 2011; 18: 63–66.

REVIEW

Inappropriate Sinus Tachycardia, Postural Orthostatic Tachycardia Syndrome, and Overlapping Syndromes

PETER A. BRADY, PHILLIP A. LOW, and WIN K. SHEN

From the Division of Cardiovascular Diseases and Internal Medicine, Mayo Clinic College of Medicine and Mayo Foundation, Rochester, Minnesota

BRADY, P.A., ET AL.: Inappropriate Sinus Tachycardia, Postural Orthostatic Tachycardia Syndrome, and Overlapping Syndromes. ***Background:*** Inappropriate sinus tachycardia (IAST) and postural orthostatic tachycardia syndrome (POTS) are syndrome complexes with some distinctive features, overlapping clinical manifestations, and potential common mechanisms. Pathogenesis of these overlapping syndromes is poorly understood. Diagnostic and therapeutic approaches have not been standardized.

Purpose: This article provides an overview of the definition, clinical presentation, and proposed mechanisms of IAST and other overlapping syndromes. A stepwise diagnostic approach is suggested. A multidisciplinary management scheme is outlined.

Methods: A MEDLINE search for English-language articles on IAST, POTS, and chronic orthostatic intolerance published up to 2005 was performed. Published data incorporated with our clinical experience were synthesized and presented in this review.

Results: The population of IAST is heterogeneous and underlying mechanisms are complex and likely multifactorial. Evidence suggests that both cardiac and extracardiac causes are plausible. Regional and limited autonomic neuropathies, at least in part, can provide a mechanism-based explanation of the cardiovascular indices and clinical symptoms in a significant number of patients with IAST. The regional abnormalities can be detected by autonomic testing. Among patients with IAST and evidence of autonomic dysregulation, an integrated autonomic, cardiovascular, and psychiatric management approach appears to be logical and rational when appropriate. Sinus node ablation could be considered in patients with persistent IAST in the absence of autonomic neuropathy and multisystem symptoms. Data from long-term outcomes are lacking.

Conclusion: The current understanding of IAST mechanisms is incomplete and management approach is not adequate. Significant effort needed in clinical research to improve therapeutic outcome. *(PACE 2005; 28:1112–1121)*

inappropriate sinus tachycardia, postural orthostatic tachycardia syndrome, chronic orthostatic intolerance, management, ablation

Introduction

Inappropriate sinus tachycardia (IAST) is characterized by paroxysmal or persistent elevation of heart rate due to an apparent sinus mechanism disproportional to the physiologic demand.[1,2] Individuals with IAST often present to physicians with diagnostic and therapeutic challenges. In part, this relates to incomplete understanding of the underlying mechanisms giving rise to the clinical syndrome, lack of precise definition, and wide-ranging, but not so effective, therapeutic interventions. Although the inappropriateness in sinus rate and frequent symptoms of palpitations bring the evaluation focus primarily on cardiovascular indices, frequent multisystem complaints from these patients suggest that IAST encompasses a heterogeneous population with extracardiovascular pathophysiologic mechanisms. Separately described, although with significant overlap in clinical presentation as in patients with IAST, is a group of patients known as postural orthostatic tachycardia syndrome (POTS), in whom the symptoms and tachycardia predominantly develop in the upright position.[3–5] Clinical presentation and underlying pathophysiology of POTS can be attributed, at least in part, to autonomic dysregulation. Although the precise relationship of IAST and POTS is not known, overlapping multisystem symptoms and autonomic abnormalities observed in selected patients with IAST[6] suggest these two syndrome complexes may share some common pathophysiologic mechanisms.

Address for reprints: Win-Kuang Shen, M.D., Mayo Clinic, 200 First Street SW, Rochester, MN 55905. E-mail: wshen@mayo.edu

Received March 22, 2005; revised April 29, 2005; accepted May 2, 2005.

The purpose of this review is to provide an overview of current understanding of IAST and overlapping syndromes, discuss diagnosis and treatment options, and offer a broad, multidisciplinary management approach in patients with apparent IAST.

Definition and Diagnosis

Inappropriate Sinus Tachycardia

IAST is a clinical syndrome with a relative or absolute increase in sinus rate out of proportion to physiological need (Table I). There is general agreement among clinicians and investigators that a heart rate exceeding 90–100 beats per minute (bpm) at rest or with minimal physiologic challenge is "inappropriate." On the surface electrocardiogram (ECG), the P-wave morphology during tachycardia is nearly identical to that during normal sinus rhythm. On a 24-hour Holter monitor, the mean heart rate exceeds 95 bpm, a daytime resting heart rate exceeds 95 bpm, or an increase in sinus rate from supine to upright position of more than 25–30 bpm.[7] Although these electrocardiographic and heart rate features provide some quantifiable parameters for IAST, the diagnosis is not quite straightforward and nor are the underlying mechanisms clearly defined. The clinical manifestations of this syndrome are diverse, and the epidemiology of this patient population has not been well defined. Patients are primarily young women (15–50 years of age), and clinical symptoms range from intermittent palpitations to multisystem complaints. The association of IAST patients with health professional workers has been recognized. The spectrum and list of common symptoms includes palpitations, lightheadedness, presyncope, syncope, exercise intolerance, easy fatigue, dyspnea, chest pain, myalgia, headache, abdominal discomfort, anxiety, and depression. Although it is usually one or more of these symptoms that bring a patient to medical attention, reproduction and correlation of symptoms, activity, and heart rate can be very challenging.

The underlying mechanisms of IAST are not well defined. Enhanced automaticity of the sinus node,[8] altered autonomic responses manifest as increased sympathetic tone, either directly or via sympathetic receptor hypersensitivity or blunted parasympathetic tone,[9,10] and impairment of baroreflex sensitivity[8] are several proposed potential mechanisms. The extent to which each of these mechanisms contributes to tachycardia and associated symptoms is unknown. In 6 patients with IAST (5 patients had normal resting heart rate), the intrinsic heart rate increased [based on the suggested formula of expected intrinsic heart rate = 118 − (0.57 × Age)] after autonomic blockade.[8] Analysis of heart rate variability showed a normal sympathovagal balance. These patients had marked increased sensitivity to isoproterenol

Table I.

IAST and POTS: Definition, Clinical Presentation, and Proposed Mechanisms

	IAST	POTS
Heart rate	"Inappropriate" for physiologic need	Persistent increase >30 bpm or absolute rate >120 bpm within 10 minutes when moving from supine to upright position in the absence of orthostatic hypotension
	>90–100 bpm at rest or with minimal exertion mean > 95 bpm on Holter	
Symptoms*	Frequent multisystem	Frequent multisystem
Proposed mechanisms	↑ Sinus node automaticity ↑ Cardiac sympathetic tone ↑ Cardiac sympathetic receptor sensitivity Blunted cardiac para-sympathetic tone Subtle or regional autonomic dysregulation overlapping with POTS	Length-dependent autonomic neuropathy Venous pooling α-hyposensitivity β-hypersensitivity Baroreceptor dysfunction Hypovolemia Brainstem dysregulation

IAST = Inappropriate sinus tachycardia; POTS = Postural orthostatic tachycardia syndrome.
*See Table II and text for discussion.

and a blunted response to vagal stimulation. These observations suggested that enhanced intrinsic sinus node automaticity was a major component of the underlying pathogenesis. In another report of 7 patients with IAST presenting with persistent sinus tachycardia,[9] only 1 patient had increased intrinsic heart rate after autonomic blockade. Excessive sympathetic tone, reflected by the marked propranolol-mediated slowing of the sinus rate, was observed in 2 patients. Five patients had impaired vagal reflexes, as shown by blunted atropine-mediated tachycardia. IAST was probably a result of sympathovagal imbalance. These varied observations highlight the heterogeneity of presentation among these patients. The focus of these investigations was on a primary cardiac mechanism of IAST; extracardiac mechanisms or potential causes of a secondary (reflex) sinus tachycardia were not explored in these investigations. In a selected IAST patient population undergoing sinus node ablation, we observed that autonomic function profiles determined by autonomic laboratory testing were highly suggestive of the presence of an extracardiac, autonomic-based pathophysiology. The symptom of palpitations and documentation of IAST were secondary phenomena to a subtle and limited systemic autonomic dysregulation.[6]

Postural Orthostatic Tachycardia Syndrome

POTS was first defined in the adult population as an increase in heart rate by more than 30 bpm or an increase to heart rate greater than 120 bpm within 10 minutes when moving from supine to the upright position (Table I).[3] Patients with similar clinical and physiologic profiles were later identified in the teenager population.[11] Patients with POTS are predominantly young women ranging in age groups from menarche to menopause. As the name of the syndrome suggests, development of tachycardia and other symptoms during upright position, and relieved by recumbence, are central features of this syndrome complex. Symptoms always include dizziness and lightheadedness. Frank syncope can occur at times, although not a predominant feature. Not infrequently, patients also report headache, tunnel vision, fatigue, neurocognitive impairment, exercise intolerance, weakness, dyspnea, tremulousness, nausea, chest or abdominal pain, sweating, anxiety, and palpitations. The intensity and frequency of symptoms is often variable and in some instances may occur and persist even when the patient is supine. Although the explanation of these symptoms is far from complete, many of the symptoms in the upright position appear to be related to a reduced cerebral blood flow.[5,12] During upright posture, some patients increase depth of respiration, causing hypopnea and cerebral vasoconstriction, resulting in symptoms of light-headedness, visual blurring, and weakness. The underlying cause of orthostatic hyperpnea remains elusive, but is likely multifactorial.

Patients with POTS do not have significant orthostatic hypotension or overt systemic autonomic neuropathy. Several mechanisms of POTS have been suggested (Table I), including length-dependent autonomic neuropathy, beta-receptor supersensitivity, alpha-receptor hypersensitivity or hyposensitivity, altered sympatho-parasympathetic balance, brain stem dysregulation, idiopathic hypovolemia, and excessive venous pooling. Approximately, one-half of patients with POTS may have a restricted form of sympathetic autonomic dysregulation that spares parasympathetic cardiovagal function.[3] A regional autonomic neuropathy that predominantly affects the lower extremities may explain the excessive venous pooling,[4,13] impaired limb arteriolar vasoconstriction[14] or microvascular filtration.[15] A selective impairment of renal sympathetic innervation may explain the decreases in plasma volume or red cell mass found in some patients.[16,17] Denervation supersensitivity may explain the cardiac beta-adrenergic hypersensitivity seen in POTS.[18,19] In some patients, with or without evidence of regional autonomic dysregulation, elevated plasma norepinephrine in the upright position has been noted.[20,21] In a preliminary investigation proposing an autoimmune mechanism, positive antibody to A_3 acetylcholine receptor (ganglionic) has been reported.[22] Although evidences of a limited autonomic dysregulation provide plausible mechanisms underlying some patients with POTS, understanding of this complex syndrome in this heterogeneous population is far from complete. The autonomic reflex system is a "closed loop." It is difficult to know whether an altered sympathetic or parasympathetic activity is primary or secondary. Some patients with POTS symptom complex and hemodynamic features do not have evidence of autonomic laboratory abnormalities. Interactions of physiologic and psychological responses are frequently suspected while difficult or impossible to differentiate.[5,23] These challenges, combining with a lack of widely available autonomic laboratory testing and of readily acceptance of any psychosomatic mechanism, continue to hinder a complete dissection of POTS pathophysiologic mechanisms.

Overlapping Syndromes

Although IAST (often described in the cardiology literature) and POTS (usually described in the neurology literature) are syndrome complexes

with some distinctive features, overlapping clinical manifestations and potential common mechanisms are apparent. In addition to having many clinical symptoms in common, the "inappropriateness" of heart rate response in patients with IAST often occurs during orthostatic stress and patients with POTS may have persistent elevation of heart rate in the recumbent position. It has been a general consensus that POTS identifies a common subgroup of a large population with chronic orthostatic intolerance.[24] Other groups with similar or overlapping laboratory findings and clinical course include hyperadrenergic syndrome,[25,26] idiopathic hypovolemia,[16] sympathotonic orthostatic hypotension,[27] and mitral valve prolapse syndrome.[28] The mechanism of persistent fatigue observed in patients with chronic orthostatic intolerance is not known. It has been reported that evidence for POTS in patients with chronic fatigue syndrome is as often as in 25–50% cases.[11,29,30] In the authors' opinion, the relationship of IAST, chronic orthostatic intolerance and chronic fatigue syndrome could be illustrated in Figure 1. Distinguishable features are present among these groups with overlapping clinical presentation and possible pathophysiologic mechanisms. POTS is a common, but not the only form of chronic orthostatic intolerance.

Evaluation

The attention and focus on cardiovascular assessment in patients with apparent IAST usually occur during the course of evaluation because symptoms of palpitations, light-headedness, occasional syncope, and recorded intermittent or persistent sinus tachycardia. A "standard" diagnostic approach to patients with possible IAST has not been developed. A practical and stepwise evaluation will be discussed in this review with the objectives to investigate potential mechanisms and to utilize the laboratory finding to guide therapy in patients with IAST.

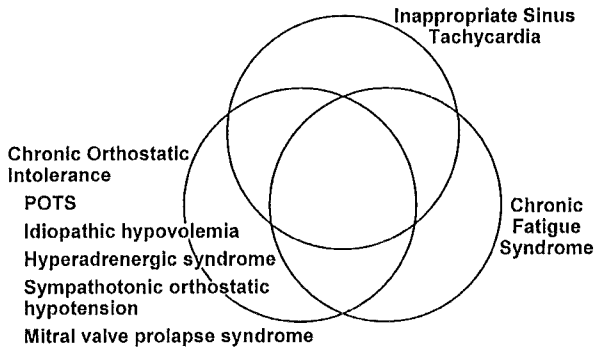

Figure 1. *Suggested relationships of IAST and other overlapping syndromes (please see text for further discussion).*

Establishing Diagnosis

A thorough history and physical examination is required to gain the appreciation whether the palpitation is an isolated and predominant feature of the patient's presentation or is one of many systemic complaints. Documentation of sinus tachycardia is required and can usually be made by a combination of noninvasive electrocardiographic testing modalities. A 12-lead ECG may or may not always record tachycardia as it is performed in the supine position at rest. It should be routinely performed, however, as the 12-lead ECG provides the standard assessment of P-wave morphology and estimates the origin of atrial depolarization. A 24-hour Holter monitoring is required and useful to determine the mean heart rate, fluctuation according to activities, limited P-wave morphology from three-standard leads, and correlation of symptoms to rate and rhythm. Additional heart rate assessment could be considered on an elective basis including an ambulatory event loop recorder to correlate heart rate to symptoms. A treadmill exercise test could be useful to assess heart rate response to activity, to correlate with symptoms and to assess conditioning and deconditioning. A prolonged tilt table test (>20 minutes) is not usually required unless the patient has recurrent and unexplained syncope or when reproduction of subjective symptoms and hemodynamic indices is desired. A tilt table testing of a shorter duration (up to 10 minutes) as a part of autonomic assessment to orthostatic stress is routinely performed in the autonomic laboratory at our center (see discussion below). The diagnosis of IAST is suspected when sinus tachycardia, inappropriate for the physiologic demand, is repeatedly documented. In the authors' experience,[2] heart rate patterns from Holter monitor among patients with IAST can be broadly categorized into three groups (Fig. 2): (1) physiologic or normal heart rate at rest (<85 bpm) with inappropriate tachycardia response to physiologic demand; (2) moderately elevated resting heart rate (exceeding 85 bpm) with accentuated (inappropriate) heart rate response to minimal exertion; (3) persistently and marked elevation (inappropriate) of sinus rate with resting heart rate or mean heart rate exceeding 95 bpm with graded heart rate response to activity. Clinically, group 2 and 3 appear to be more common. Although the characterization of the heart rate trends is rather qualitative and simple, combining with patient's symptoms, it could be useful in making therapeutic decisions, and in guiding and assessing response to therapy.

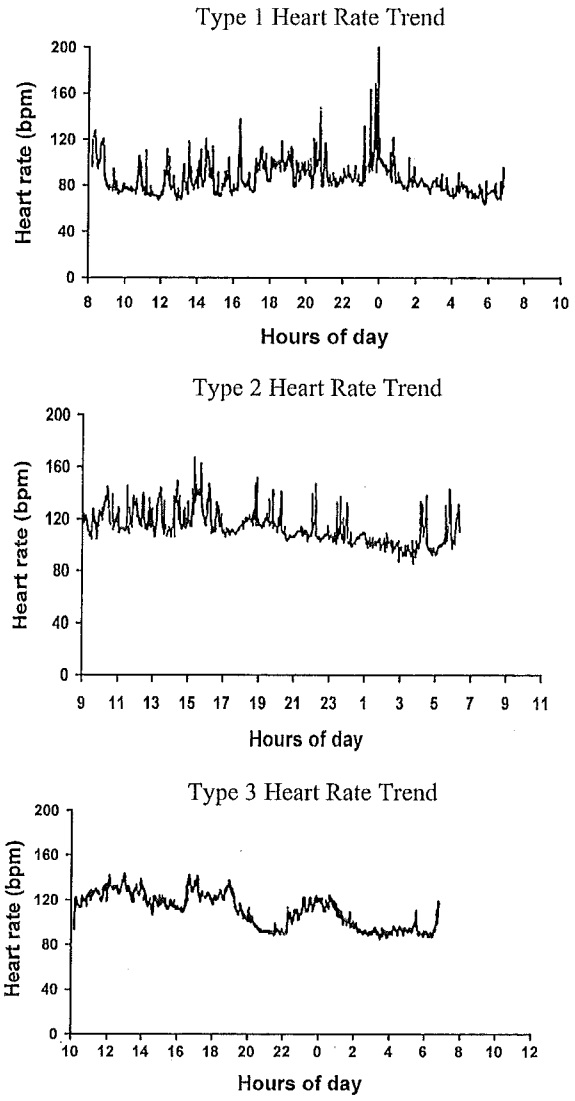

Figure 2. *Heart rate trend plot from Holter monitoring outlining three general patterns in patients with IAST (please see text for discussion: (with permission, modified from Ref. 2)).*

Excluding Secondary Causes of Sinus Tachycardia

While the documentation of IAST is being made, secondary causes of sinus tachycardia must be excluded by conducting a thorough general medical evaluation. Anemia, infection, fever, and endocrinological abnormalities should be examined. The following blood tests are considered as screening and routine: complete blood count, fasting blood glucose, and thyroid function screen. Assessment of orthostatic plasma norepinephrine, urinary metanephrines, and 24-hour urinary sodium excretion could be considered on a selected basis. Conditions such as diabetic neuropathy, hyperthyroidism, Cushing's disease, pheochromocytoma, carcinoid, and other endocrinologic abnormalities should be considered in the differential diagnosis. An echocardiographic examination is usually recommended to exclude any significant structural cardiopulmonary abnormalities. It should be emphasized that the left ventricular function is always normal in patients with IAST, a potential discriminator compared to other mechanisms of tachycardia that may lead to tachycardia induced cardiomyopathy or sinus tachycardia may be secondary to preexisting compromised cardiac function.

Assessing Autonomic Contribution

Following the documentation of IAST and after secondary causes are excluded, an autonomic evaluation including screening for autonomic dysfunction and autonomic neurological consultation is considered obligatory when the constellations of systemic and postural symptoms are present. A complete discussion of autonomic testing is beyond the scope of this review. A brief summary of autonomic screening and observations relevant to patients with IAST will be provided. For a more detailed description on autonomic testing, readers are referred to a recent comprehensive review.[31]

The general concepts of targeted autonomic function assessment and the components of laboratory testing are summarized in Table II. The screening tests of autonomic function are grouped into three categories: sudomotor function, cardiovagal regulation, and vasomotor regulation. Sudomotor function (postganglionic sympathetic pathway) is assessed with the quantitative sudomotor axon reflex test (QSART), which quantifies the amount of sweating upon acetylcholine challenge. A reduced or absent sweat response indicates postganglionic sympathetic sudomotor failure. In selected IAST patients with POTS

Table II.

Autonomic Reflex Screen: General Concepts

Postganglionic Sudomotor Failure
Abnormal QSART
Cardiovagal dysfunction
Reduced HRR deep breathing and Valsalva ratio
Adrenergic dysfunction
Abnormal phase II, IV response during Valsalva maneuver and responses during tilt

QSART = quantitative sudomotor axon reflex test.
HRR = heart rate range.

features, abnormal QSART is present in a length-dependent manner suggestive of distal small-fiber neuropathy. When QSART is abnormal, the degree and extent of sudomotor dysfunction can be further determined by the thermoregulatory sweat test (TST). Cardiovagal regulation is estimated by heart rate response to deep breathing (HR_{DB}) and the Valsalva maneuver. In our autonomic reflex laboratory, HR_{DB} is determined by the heart rate range (maximum–minimum) during six cycles of breathing per minute (inspiratory and expiratory cycles of 5-seconds each). The Valsalva ratio (VR) is derived from the maximum heart rate generated by the Valsalva maneuver divided by the lowest heart rate occurring within 30 seconds of peak heart rate. Both HR_{DB} and VR provide indirect assessment of the vagal regulation of heart rate. The vasomotor activity is assessed by the beat-to-beat heart rate and blood pressure response to tilt and the Valsalva maneuver. During phase II of Valsalva maneuver, exaggerated early drop of blood pressure and attenuated late recovery suggest subtle vasomotor insufficiency in the absence of orthostatic hypotension. An overshoot of blood pressure during early phase IV suggests the presence of hyperadrenergic response. An example of hemodynamic responses from a patient with IAST with features of POTS is shown in Figure 3. This patient had a rather normal heart rate in the supine position at rest. In response to tilt, sustained sinus tachycardia ranging from 110–150 bpm was observed. Orthostatic hypotension was not present while pulse pressure was reduced in response to tilt. These observations are suggestive of a hyperadrenergic response. An example of a length-dependent, post-ganglionic sympathetic sudomotor neuropathy in a patient with IAST is shown in Figure 4. The TST showed a patchy hypohidrosis response pattern in the lower extremities, with a relatively normal sweat pattern in the trunk. The blood pressure and heart rate response during Valsalva maneuver in an IAST patient with a mild (without orthostatic hypotension) abnormal adrenergic vasoconstrictive response is shown in Figure 5. The blood pressure response was attenuated during phase II, suggesting impairment of vasoconstriction, whereas an exaggerated response was noted during phase IV, suggesting hyperadrenergic reactivity. Although standard techniques and normal ranges for these test results corrected for age and gender have been published,[31] routine autonomic screen testing has been limited to a few selected medical centers. In a small group of patients with IAST undergoing sinus node modification ablation, one or more abnormal autonomic test results were frequently observed.[6] The exact prevalence of autonomic dysregulation in the population of IAST at large is unknown because autonomic testing has not been routinely performed in these patients.

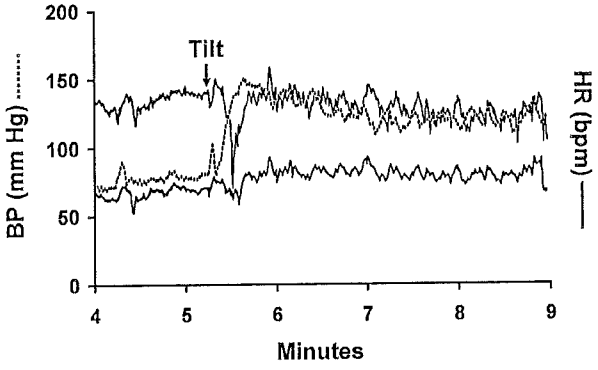

Figure 3. *Blood pressure (BP) and heart rate (HR) response during tilt table testing in a patient with IAST. Immediately after tilt, heart rate (dotted line) increased significantly and the overall systolic and diastolic pressure (solid line) remained stable. The pulse pressure was significantly reduced (with permission from Ref. 6).*

Excluding Other Supraventricular Arrhythmias

A diagnostic electrophysiologic study should be considered when the etiology or mechanism of the documented tachycardia is uncertain or when other supraventricular tachyarrhythmias are suspected. During the study, programmed stimulation is performed to exclude sinus node reentry tachycardia, atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, ectopic atrial tachycardia, and atrial tachycardia or atrial fibrillation. Several classic findings should be obtained during electrophysiologic study to confirm the diagnosis of tachycardia of a sinus origin. A gradual increase (warm-up) and decrease (cooldown) in heart rate spontaneously or during initiation and termination of isoproterenol infusion are consistent with an automatic mechanism of sinus node function. The surface P-wave morphology should be similar to that observed during sinus rhythm. During mapping, the earliest endocardial activation should be near the area of sinus node along the crista terminalis estimated from biplane fluoroscopic images, intracardiac ultrasonography, or advanced 3-D electro-anatomic techniques. The atrial depolarization sequence is always cranial-caudal along the crista terminalis. During rate changes, the site of earliest activation shifts superiorly along the crista terminalis at a faster rate and inferiorly along the crista terminalis at a slower rate.

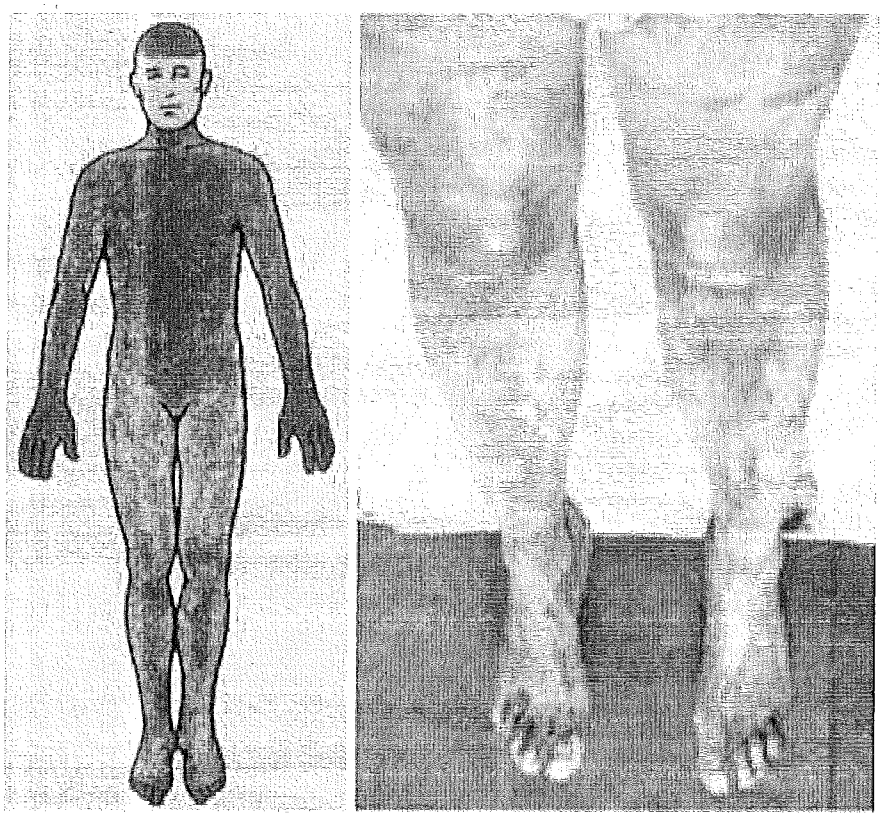

Figure 4. *Thermoregulatory sweat test shows patchy hypohydrosis of the left and right lower extremities below the knee and normal sweating elsewhere (please see text for discussion (with permission from Ref. 6)).*

Therapy and Management

IAST with POTS Features

Although physiologic patterns defined by cardiovascular and autonomic indices have the potential to refine treatment approaches, current management of these patients are far from adequate. For IAST patients with evidence of autonomic dysregulation (POTS features with multisystem symptomatology), or episodic symptom complex in the absence of a persistent and marked sinus tachycardia (type 2 and 3 Holter response), we adopted a multidisciplinary model in managing these patients with input from autonomic neurology, cardiovascular rehabilitation, and psychiatry.

Comprehensive reviews of autonomic approaches to these patients can be found in several excellent publications.[4,5,24,30,32] A summary of therapeutic targets based on mechanistic categories and suggested interventions are provided in Table III.

Sleeping with head of the bed elevated (15 degrees) and expanding of plasma volume through generous salt and fluid intake can be helpful with minimal risk in most patients. The salt intake should be between 150 and 250 mEq sodium (10–20 mg of salt). Salt intake and blood pressure are closely related. Some patients are sensitive to salt intake alone, requiring close surveillance especially in patients with known labile blood pressure. Fluid intake should be targeted

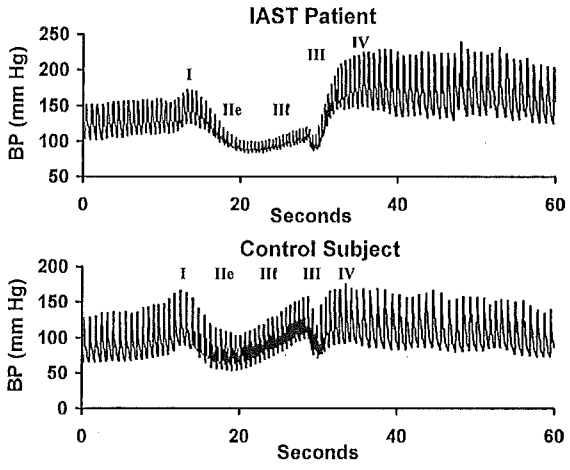

Figure 5. *During Valsalva maneuver, the blood pressure response during late phase II was attenuated, consistent with a reduction in vasoconstrictive response. The large overshoot during phase IV suggests a hyperadrenergic state (with permission from Ref. 6).*

Table III.

Integrated Management of Patients with IAST

Presumed Mechanisms	Suggested Therapy
Hypovolemia; Deconditioning	Volume expansion Fluodrocortisone Sleep with head of bed elevated Exercise prescription
Venous pooling	Volume expansion Pressure stockings Midodrine Resistance training/counter maneuvers
Peripheral adrenergic failure	Fluodrocortisone α-agonists: midodrine, methylphenidate
Hyper-adrenergic state	β-blockers (nonselective preferred)
Brainstem/central mechanism	Phenobarbital Clonidine
Depression/anxiety	Psychiatric evaluation
Refractory cases	Erythropoitin IV saline infusion
Isolated and persistent IAST*	Sinus node modification

*See text for discussion.

at 2–2.5 L/day. When evidence of hypovolemia is persistent despite liberal salt and fluid intake, fludrocortisone with a dose of 0.1 mg/day can be initiated and adjusted upward up to 1 mg/day in young patients.

Compression stockings may provide additional benefit in patients with evidence of venous pooling, although inconvenience frequently prohibits long-term use. Midodrine is efficacious in some patients. In others, supplemental octreotide may be used for periods of orthostatic decompensation. Physical counter-maneuvers appear to be beneficial for this group of patients. Some patients seem to obtain favorable outcome with a 3-month program of graduated training. Resistance training may be more beneficial than endurance training, but a systematic evaluation of outcomes is lacking.

Patients with peripheral adrenergic dysfunction, manifested as a loss or attenuated late phase II response during Valsalva maneuver or evidence of mild orthostatic hypotension, are best treated with fludrocortisone and an alpha-agonist. Midodrine appears to be the most efficacious in absorption, predictability in duration of action, and lack of central nervous system side effects. Clinical experience from other drugs such as ephedrine, phenylpropanolamine, and methophenidate has been very limited.

Evidence of beta-receptor methyl supersensitivity is usually associated with multisystem complaints. These patients often respond to but are sometimes highly sensitive to beta-antagonists. Fatigue is a common side effect in these patients. A nonselective β-blocker such as propranolol or nadolol can be started at low dose, titrated upward according to heart rate response and tolerance over 2–4 weeks. Selection of a selective β-blocker or lipophilic profile can be individualized.

It is logical to consider assessment of psychiatric status in patients with overt psychosomatic complaints. Such approach should lead to a more rational integrated management of these complex patients although the clinical dilemma is confounded by the frequent rejection of any psychiatric etiology by many patients.

Role of Sinus Node Ablation and Modification

The role of sinus node ablation and modification in patients with IAST has not been well defined. The body of literature is small and controversial. An electrophysiological approach of total ablation or modification of sinus node function in the mid 90s to early 2000 raised the possibility and optimism that the sinus node could be effectively slowed or obliterated by radiofrequency ablation.[33–36] Although short-term success rates were quite favorable ranging from 76–100%, long-term outcomes were either incomplete or suboptimal. A follow-up report in an abstract form indicated that sustained improvement of tachycardia symptoms was achieved in only 8 (36%) of 22 patients during a mean follow-up of 8 ± 5 months following sinus node ablation.[37] The need for a pacemaker and procedural-related complications, including phrenic nerve injury and superior vena cava obstruction, has been noted in some patients. In these studies, autonomic testing was not performed.

In our study of seven patients with IAST and features of POTS confirmed by autonomic testing, the feasibility and immediate successful outcome of sinus rate reduction as reported by other investigators were confirmed.[6] However, none obtained a long-term favorable outcome. Most of the cardiac and extracardiac symptoms persisted despite documented slower heart rate by Holter monitoring and treadmill exercise during follow-up. The autonomic score index, primarily based on symptoms mediated by the autonomic nervous system, showed no significant improvement. These findings strongly suggest that the primary pathogenesis

underlying symptoms in patients with IAST with POTS features is autonomic in origin. IAST and symptoms of palpitations are merely secondary manifestation of an autonomic neuropathic process.

All ablation studies have been subjected to significant bias because patients were highly selected, control groups were lacking, and numbers were small. In light of poor long-term outcomes in our experience, we do not recommend sinus node modification in patients with IAST with POTS features. However, we do recognize that there is a small group of patients with IAST with minimal extracardiac symptoms and persistently elevated heart rate (Type 3 heart rate pattern on Holter). Sinus node modification could be helpful, although long-term clinical response of these patients to ablation remains to be determined.

The overall prognosis of patients with IAST is unclear. Among patients with POTS with frequent, persistent, and at least moderately severe symptoms with prolonged duration, symptoms were self-resolving in the majority of patients.[38] Among 40 patients with follow-up, 80% reported improvement in symptoms, with 60% returning to a functionally normal or near-normal level after medical therapy. None of these patients had sinus node ablation.

Conclusion and Future Direction

The current understanding of IAST mechanisms is incomplete and management approach is not adequate. In patients with IAST, it is critical to determine the autonomic profile in that, as the authors propose, autonomic abnormalities are frequently present and definable by autonomic testing. An integrated model with a multidisciplinary management approach is logical. Development of new drugs, specifically targeting the pacemaker current in the sinus node,[39] could be of interest in treating IAST patients with minimal extracardiac symptoms. A mechanism-based diagnostic scheme has the potential to improve therapeutic approaches and outcomes. Additional efforts will be required to bring the research findings to clinical practice.

Acknowledgments: Dr. W. K. Shen receives support from the National Institute of Health (P50NS 32352–7 and P50NS 32352–8). We acknowledge the excellent secretarial assistance from Mrs. Kathleen Budensiek and Mrs. Kasee Stai.

References

1. Krahn AD, Yee R, Klein GJ, Morillo C. Inappropriate sinus tachycardia: Evaluation and therapy. J Cardiovasc Electrophysiol 1995; 6:1124–1128.
2. Shen WK. Modification and Ablation for Inappropriate Sinus Tachycardia: Current Status. Card Electrophysiol Rev 2002; 6:349–355.
3. Schondorf R, Low P. Idiopathic postural orthostatic tachycardia syndrome: An attenuated form of acute pan dysautonomia. Neurology 1993; 43:132–137.
4. Low PA, Opfer-Gehrking TL, Textor SC, Benarroch EE, Shen WK, Schondorf R, Suarez GA, et al. Postural tachycardia syndrome (POTS). Neurology 1995; 45:S19–S25.
5. Low PA, Schondorf R, Rummans TA. Why do patients have orthostatic symptoms in POTS? Clin Auton Res 2001; 11:223–224.
6. Shen WK, Low PA, Jahangir A, Munger TM, Friedman PA, Osborn MJ, Stanton MS, et al. Is sinus node modification appropriate for inappropriate sinus tachycardia with features of postural orthostatic tachycardia syndrome? Pacing Clin Electrophysiol 2001; 24:217–230.
7. Castellanos A, Moleiro F, Chakko S, Acosta H, Huikuri H, Mitrani RD, Myerburg RJ. Heart rate variability in inappropriate sinus tachycardia. Am J Cardiol 1998; 82:531–534.
8. Morillo CA, Klein GJ, Thakurrk, Li H, Zadini M, Yee R. Mechanisms of inappropriate sinus tachycardia: Role of sympathovagal imbalance. Circulation 1994; 90:873–877.
9. Bauernfeind RA, Amat-Y-Leon F, Dhingra RC, Kehoe R, Wyndham C, Rosen KM. Chronic nonparoxysmal sinus tachycardia in otherwise healthy persons. Ann Intern Med 1979; 91:702–710.
10. Sgarbossa EB, Yamanouchi Y, Rejna TG, Miller DP, Morant VA, Pinski SL. Autonomic imbalance in patients with inappropriate sinus tachycardia. (abstract) Am Coll Cardiol 1995; 25: 193A.
11. Stewart JM, Gewitz MH, Weldon A, Munoz J. Patterns of orthostatic intolerance: The orthostatic tachycardia syndrome and adolescent chronic fatigue. J Pediatr 1999; 135:218–225.
12. Novak P, Novak V, Petty G, Opfer-Gehrking T, Low PA. Hyperventilation contributes to an abnormal cerebral blood flow in postural tachycardia syndrome (POTS). Neurology 1997; 48:A148.
13. Freeman R, Lirofonis V, Farquhar WB, Risk M. Limb venous compliance in patients with idiopathic orthostatic intolerance and postural tachycardia. J Appl Physiol 2002; 93:636–644.
14. Stewart JM. Pooling in chronic orthostatic intolerance: Arterial vasoconstrictive but not venous compliance defects. Circulation 2002; 105:2274–2281.
15. Stewart JM. Microvascular filtration is increased in postural tachycardia syndrome. Circulation 2003; 107:2816–2822.
16. Fouad FM, Tadena-Thome L, Bravo EL, Tarazi RC. Idiopathic hypovolemia. Ann Intern Med 1986; 104:298–303.
17. Jacob G, Robertson D, Mosqueda-Garcia R, Ertl AC, Robertson RM, Biaggioni I. Hypovolemia in syncope and orthostatic intolerance role of the renin-angiotensin system. Am J Med 1997; 103:128–133.
18. Goldstein DS, Holmes C, Frank SM, Dendi R, Cannon RO III, Sharabi Y, Esler MD, et al. Cardiac sympathetic dysautonomia in chronic orthostatic intolerance syndromes. Circulation 2002; 106:2358–2365.
19. Frohlich ED, Tarazi RC, Dustan HP. Hyperdynamic beta-adregergic circulatory state: Increased beta-receptor responsiveness. Arch Intern Med 1969; 123:1–7.
20. Jacob G, Costa F, Shannon JR, Robertson RM, Wathen M, Stein M, et al. The neuropathic postural tachycardia syndrome. N Engl J Med 2000; 343:1008–1014.
21. Jordan J, Shannon JR, Diedrich A, Black BK, Robertson D. Increased sympathetic activation in idiopathic orthostatic intolerance: Role of systemic adrenoreceptor sensitivity. Hypertension 2002; 39:173–178.
22. Vernino S, Low PA, Fealey RD, Stewart JD, Farrugia G, Lennon VA. Autoantibodies to ganglionic acetylcholine receptors in autoimmune autonomic neuropathies. N Engl J Med 2000; 343:847–855.
23. Benrud-Larson LM, Dewar MS, Sandroni P, Rummans TA, Haythornthwaite JA, and Low PA. Quality of life in patients with postural tachycardia syndrome. Mayo Clin Proc 2002; 77(6):531–537.
24. Robertson D. The epidemic of orthostatic tachycardia and orthostatic intolerance. Am J Med Sci 1999; 317:75–77.
25. Streeten DH, Anderson GH Jr, Richardson R, Thomas FD. Abnormal orthostatic changes in blood pressure and heart rate in subjects with intact sympathetic nervous function: Evidence for excessive venous pooling. J Lab Clin Med 1988; 111:326–335.
26. Streeten DH. Pathogenesis of hyperadrenergic orthostatic hypotension: evidence of disordered venous innervation exclusively in the lower limbs. J Clin Invest 1990; 86:1582–1588.

27. Hoeldtke RD, Dworkin GE, Gaspar SR, Israel BC. Sympathotonic orthostatic hypotension: A report of four cases. Neurology 1989; 39:34–40.
28. Coghlan HC, Phares P, Cowley M, Copley D, James TN. Dysautonomia in mitral valve prolapse. Am J Med 1979; 67:236–244.
29. Freeman R, Komaroff AL. Does the chronic fatigue syndrome involve the autonomic nervous system? Am J Med 1997; 102:357–364.
30. Stewart JM. Chronic orthostatic intolerance and the postural tachycardia syndrome (POTS). J Pediatr 2004; 145:725–730.
31. Low PA. Testing the autonomic nervous system. Semin Neurol 2003; 23:407–421.
32. Grubb BP, Kanjwal MY, Kosinski DJ. Postural orthostatic tachycardia syndrome: Current concepts in pathophysiology diagnose and management. J Int Card Electrophysiol 2001; 5:11–18.
33. Jayaprakash S, Sparks PB, Vohra J. Inappropriate sinus tachycardia (IST): Management by radiofrequency modification of sinus node. Aust N Z J Med 1997; 27:391–397.
34. Lee RJ, Kalman JM, Fitzpatrick AP, Epstein LM, Fisher WG, Olgin JE, Lesh MD, Scheinman MM. Radiofrequency catheter modification of the sinus node for "inappropriate" sinus tachycardia. Circulation 1995; 92:2929–2928.
35. Man KC, Knight B, Tse HF, Pelosi F, Michaud GF, Fleming M, Strickberger SA, Morady F. Radiofrequency catheter ablation of inappropriate sinus tachycardia guided by activation mapping. J Am Coll Cardiol 2000; 35:451–457.
36. Marrouche NF, Beheiry S, Tomassoni G, Cole C, Bash D, Dresing T, Saliba W, et al. Three-dimensional nonfluroscopic mapping and ablation in inappropriate sinus tachycardia: Procedural strategies and long-term outcome. J Am Coll Cardiol 2002; 39:1046–1054.
37. Shinbane JS, Lesh MD, Scheinman MN, Wood K, Evans GT Jr, Saxon LA, Barron H, Kalman JM, Lee RJ. Long-term follow up after radiofrequency sinus node modification for inappropriate sinus tachycardia. (abstract) J Am Coll Cardiol 1997; 29(Suppl. A):199A.
38. Sandroni P, Opfer-Gehrking TL, McPhee BR, Low PA. Postural tachycardia syndrome: Clinical features and follow-up story. Mayo Clin Proc 1999; 74(11):1106–1110.
39. Nemec J, Shen WK. Antiarrhythmic drugs: New agents and evolving concepts. Expert Opin Investig Drugs 2003; 12(3):435–453.

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Mechanism of 'inappropriate' sinus tachycardia. Role of sympathovagal balance.

C A Morillo, G J Klein, R K Thakur, H Li, M Zardini and R Yee

Circulation. 1994;90:873-877
doi: 10.1161/01.CIR.90.2.873
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

Mechanism of 'Inappropriate' Sinus Tachycardia

Role of Sympathovagal Balance

Carlos A. Morillo, MD; George J. Klein, MD; Ranjan K. Thakur, MD; Huagui Li, MD, PhD; Marco Zardini, MD; Raymond Yee, MD

Background "Inappropriate" sinus tachycardia (IST) is an uncommon and poorly defined atrial tachycardia characterized by inappropriate tachycardia and exaggerated acceleration of heart rate with "normal" P wave. The mechanism of this tachycardia is unknown. The purpose of the present study was to determine the role of autonomic balance in the genesis of IST.

Methods and Results Six female patients aged 23 to 38 years with IST and 10 age- and sex-matched control subjects were assessed with the following autonomic function tests: (1) sympathovagal balance to the sinus node assessed by calculating the LF/HF (low frequency/high frequency) ratio using power spectral analysis both in the supine position and after 10 minutes of head-up tilt to 60°, (2) cardiovagal reflex assessed by cold face test (CFT), (3) β-adrenergic sensitivity as determined by calculating isoproterenol dose-response curves and isoproterenol chronotropic dose 25 (CD_{25}), and (4) intrinsic heart rate (IHR) assessed after autonomic blockade with atropine 0.04 mg/kg and propranolol 0.2 mg/kg administered as an intravenous bolus. No significant differences in the LF/HF ratio both in the supine position (2.8±0.3 versus 2.6±0.4) and during upright tilt (8.7±1.3 versus 8.5±0.5) were observed between control subjects and IST patients. Cardiovagal response to CFT was markedly depressed in all patients (6.3% IST patients versus 24.2% control subjects, $P<.001$). β-Adrenergic hypersensitivity to isoproterenol was noted in all patients (mean CD_{25}, 0.29±0.10 μg IST patients versus 1.27±0.4 μg control subjects; $P<.001$), and high IHR was noted in all cases. The patients were treated with high doses of β-blockers with adequate short-term control. Radiofrequency catheter ablation of the sinus node area was performed in one drug-refractory patient.

Conclusions These findings suggest that the mechanism leading to IST is related to a primary sinus node abnormality characterized by a high IHR, depressed efferent cardiovagal reflex, and β-adrenergic hypersensitivity. (***Circulation.*** **1994; 90:873-877.)**

Key Words • tachycardia • autonomic function • sinus node

Inappropriate" sinus tachycardia (IST; nonparoxysmal sinus tachycardia, permanent sinus tachycardia) is an atrial tachycardia characterized by inappropriate tachycardia and exaggerated acceleration of heart rate during physiological stresses. The P wave morphology suggests origin in or very close to the sinus node.[1-4] The mechanism leading to an exaggerated response of the sinus node to minimal physiological stress is incompletely understood. It is not clear whether the abnormality is an abnormal sinus node (or atrial pacemaker) or abnormal autonomic function with a normal sinus node. This study investigated the autonomic balance of the sinus node in 6 consecutive patients with IST.

Methods

Study Population

The study population consisted of 6 female patients aged 23 to 38 years with a history of tachycardia for a period of 3 or more months and 10 female control subjects aged 22 to 39 years. IST was defined by the following criteria[1]: (1) atrial rate of ≥100 beats per minute at rest or triggered by minimal physiological stress, (2) "normal" P wave axis and morphology during tachycardia documented electrocardiographically, and (3) absence of orthostatic hypotension, diabetes mellitus, hyperthyroidism, or drug abuse. Verbal and written informed consent was obtained in all patients.

Clinical and Laboratory Examinations

All patients had a physical and neurological examination, a 12-lead ECG, ambulatory ECG monitoring for 24 to 48 hours, and a two-dimensional echocardiogram. Thyroid function and glucose levels were assessed in all patients. Exercise stress test was assessed in 4 patients.

Autonomic Function Tests

Subjects were studied in the postabsorptive state. All studies were performed at 8:30 AM. An intravenous line was inserted, and 5% dextrose in normal saline was started at a rate of 20 mL/hr. Continuous noninvasive assessment of blood pressure (Finapress, Ohmeda 2300) and ECG limb leads I, II, and III were recorded on a Graphix Thermal Array Corder (WR 3600). Two ECG leads were continuously recorded with a tape recorder (Zymed Tritrak 1100-5) for further analysis.

Sympathovagal Balance

Subjects were allowed 15 minutes in the supine position for stabilization. Sympathovagal balance in the supine position and during orthostatic stress was assessed by power spectral analysis of heart rate variability obtained from the tape-recorded ECG.[5-10] Heart rate variability was assessed after 10 minutes in the supine position and after 10 minutes of upright

Received January 26, 1994; revision accepted April 15, 1994.

From the Department of Medicine, University of Western Ontario, London, Ontario, Canada.

Correspondence to Dr C.A. Morillo, Hunter Holmes McGuire VA Medical Center, Cardiovascular Physiology, 1201 Broad Rock Blvd, Richmond, VA 23249.

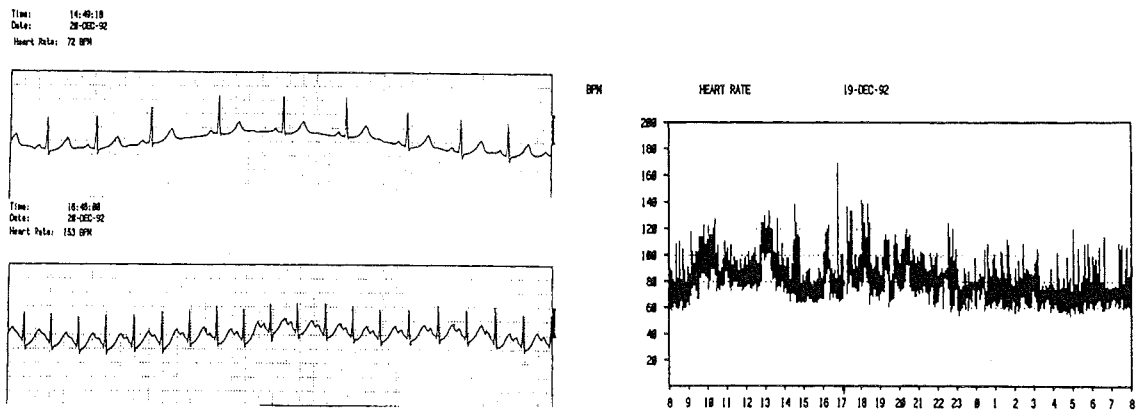

FIG 1. Left, Ambulatory ECG. Top recording shows resting heart rate of 72 beats per minute (BPM). Sinus tachycardia of 153 beats per minute (bottom) evidenced by the presence of a positive P wave preceding each QRS complex was triggered after assuming the upright position. Right, Hourly trends in heart rate obtained from a 24-hour ambulatory ECG recording from the same patient. Heart rate ranged between 58 and 172 beats per minute.

head-up tilt on an electronically driven table with footboard support to 60°. All tapes were digitally processed and manually scanned with a Zymed 1210 Holter system. Power spectral density was calculated by a fast Fourier transform algorithm producing a 512-point spectrum for the 0.01- to 1.0-Hz frequency band. Low-frequency (LF) power (0.04 to 0.15 Hz) and high-frequency (HF) power (0.15 to 0.5 Hz) were obtained, and the sympathovagal balance expressed as the LF/HF ratio was calculated.[5-10] Ten age-matched (mean, 29±6 years), sex-matched healthy volunteers from our laboratory were used as control subjects.[11]

Cold Face Test

The cardiovagal reflex was evaluated by exploring the trigeminal-vagal response both in the study population as well as in the 10 control subjects. Bilateral cold pads (0°C) were applied over the ophthalmic branches of the trigeminal nerve for a period of 1 minute.[12-14] Baseline heart rate was derived from the mean of the values recorded in the 2 minutes preceding the cold face test (CFT). The minimum heart rate during CFT was detected, and mean heart rate was calculated from 10 sinus beats (5 beats preceding and 5 beats after minimum heart rate). The magnitude of heart rate change is expressed as the percent reduction from mean baseline heart rate. The methodology and validation of this test has been previously reported by our laboratory and by others.[12-15]

Isoproterenol Sensitivity Test

β-Adrenergic sensitivity was assessed by calculating isoproterenol dose-response curves in each patient.[16] Isoproterenol hydrochloride was given as a rapid 1-mL bolus. The initial dose used was always 0.25 μg and was thereafter doubled (0.5, 1.0, 2.0, and 4.0 μg) until an increase in heart rate of 35 beats per minute or a peak heart rate of 150 beats per minute was achieved. Ten minutes was allowed between each injection to allow return to baseline heart rate. The peak heart rate before and after each injection was calculated from the three shortest RR intervals of the ECG. Isoproterenol chronotropic dose 25 (CD_{25}) was defined as the dose necessary to achieve an increase in heart rate of 25 beats per minute. The 10 control subjects underwent the same protocol, and data were pooled with that acquired from 5 healthy subjects previously reported.[16]

Intrinsic Heart Rate

Intrinsic heart rate (IHR) was assessed after bolus injection of propranolol 0.2 mg/kg and atropine 0.04 mg/kg.[17] The IHR observed was compared with the predicted value for each patient by the formula IHR=118.1−(0.57×age).[17,18]

Statistical Analysis

Data are presented as mean±SD. Comparison between groups was assessed by one-way ANOVA. Continuous variables were assessed by a two-tailed unpaired *t* test. Differences were considered significant if the null hypothesis was rejected at the level of $P<.05$.

Results

All patients had normal physical and neurological examination. Thyroid function, glucose levels, and two-dimensional echocardiogram were normal in all patients. Heart rate response to low-grade exercise was markedly enhanced in the 4 patients assessed by exercise test, achieving a heart rate between 130 and 160 beats per minute (stage I Bruce protocol). Heart rates during tachycardia documented by Holter recordings in all patients varied between 140 and 185 beats per minute (Fig 1). Heart rate ranges during Holter recordings and heart rate response to head-up tilt and exercise treadmill are summarized in Table 1.

Autonomic Function Tests

Results of the autonomic function tests are shown in Table 2.

Sympathovagal Balance

Sympathovagal balance to the sinus node expressed as the LF/HF ratio in the supine position (2.8±0.3 versus 2.6±0.4) and after 10 minutes of upright tilt (8.7±1.3 versus 8.5±0.8) did not differ between control subjects and IST patients (P=NS).

Cold Face Test

The cardiovagal reflex was markedly abnormal in all patients (Table 2). Minor changes in percent heart rate were achieved: 6.3±2.1% in IST patients versus 24±8.5% in control subjects ($P<.001$), suggesting an impaired response of the sinus node to vagal stimulation.

Isoproterenol Sensitivity Test

β-Adrenergic hypersensitivity was observed in all patients. Dose-response curves showed an increased sensitivity to incremental dosages of isoproterenol (Fig 2). Similarly, CD_{25} was distinctively lower in IST patients than the mean dose required to achieve the same

TABLE 1. Heart Rate Characteristics

Patient	Awk Av HR	Asl Av HR	HR Rng (24 h)	HRS, bpm	HRT (1 min)	HRT (5 min)	BPS, mm Hg	BPT, mm Hg	ET-HR (1 min)
1	83	74	55-152	78	120	134	110/70	115/75	NA
2	74	68	58-140	68	130	140	120/85	125/88	125
3	78	70	62-145	78	110	118	103/68	110/75	118
4	84	76	58-168	88	145	154	108/62	115/72	128
5	94	88	70-155	96	140	155	105/72	110/78	134
6	105	94	88-185	106	152	164	105/80	110/88	NA

Asl indicates asleep; Av, average; Awk, awake; bpm, beats per minute; BPS, blood pressure supine; BPT, blood pressure tilt; ET-HR, exercise treadmill heart rate; HR, heart rate; HRS, heart rate supine; HRT, heart rate tilt; NA, not available; and Rng, range.

end point in healthy control subjects (0.29±0.10 μg in IST patients versus 1.27±0.4 μg in control subjects, $P<.001$).

Intrinsic Heart Rate

IHR observed was remarkably higher (±2 SD) than predicted in all patients (Fig 3). Despite complete autonomic denervation, response of the sinus node was significantly increased.

Therapy

All patients received propranolol (160 to 320 mg) or atenolol (100 to 200 mg) daily. Patients were followed for a period of 4 to 8 months. Only one patient (patient 6) persisted with IST. At electrophysiological study, sinus tachycardia at a rate of 145 beats per minute was induced by an isoproterenol infusion at a rate of 0.5 μg/min. A high to low atrial activation pattern originating in the area of the sinus node was documented. Earliest site of activation was mapped to the high posterolateral right atrium below the superior vena cava and right atrial junction. Atrial activation at this site preceded the surface P wave by 25 milliseconds, with the latest activation site recorded in the low lateral right atrium. Tachycardia was neither induced nor terminated by critically timed atrial extrastimuli or atrial pacing. Twenty radiofrequency energy applications were delivered to this area at a power level of 15 to 25 W, with a duration ranging between 30 and 60 seconds. Radiofrequency energy application at this site was associated with transient sinoatrial exit block and junctional rhythm at the end of the procedure. Normal sinus rhythm was restored 48 hours after the procedure. After ablation, autonomic function tests demonstrated a normal β-adrenergic response and an IHR of 103 beats per minute compared with 140 beats per minute before ablation. Power spectral analysis of heart rate variability in the supine position and during 60° tilt remained unchanged. In contrast, CFT showed a tendency toward normalization (5.1% before ablation versus 12% after ablation). A 48-hour Holter monitor assessed 3 months after ablation documented resting heart rates ranging between 38 and 128 beats per minute. The patient has remained free of tachycardia for over 10 months.

Discussion

IST is a rare cause of supraventricular tachycardia that may be associated with incapacitating symptoms requiring aggressive therapy.[1-4] IST may be related to one or a combination of the following mechanisms: (1) ectopic atrial focus in the sinus node region, (2) normal sinus node with increased sympathetic tone or failure to respond to vagal stimulation, or (3) intrinsic abnormality of the sinus node. The present study explored the role of autonomic balance in 6 patients meeting clinical criteria for IST.[1-4]

Sympathovagal balance at rest and after upright tilt was evaluated by power spectral analysis of heart rate

TABLE 2. Autonomic Function Tests

Patient	Age, y	LF/HF S:T	IHR Pr	IHR Obs	NR, bpm	CFT, %HR	CD_{25}, μg
1	23	2.6:8.1	100	125	84-116	2.4	0.50
2	38	2.4:8.2	96	122	80-112	8.8	0.25
3	23	2.6:8.3	104	134	88-120	8.5	0.25
4	28	2.8:8.5	101	125	85-117	7.2	0.25
5	26	3.2:9.8	103	130	87-119	5.8	0.25
6	24	2.2:8.4	104	140	88-120	5.1	0.25
Mean	27±5	2.6:8.5	101	129	...	6.3±2.1	0.29±0.1
Control subjects	29±6	2.8:8.7	...	...	...	24.2±8.5	1.27±0.4

bpm indicates beats per minute; CD_{25}, chronotropic dose 25; CFT, cold face test; HR, heart rate; IHR, intrinsic heart rate; LF/HF, low-frequency/high-frequency ratio; NR, normal heart rate range; Obs, observed heart rate; Pr, predicted heart rate; S, supine position; and T, upright tilt.

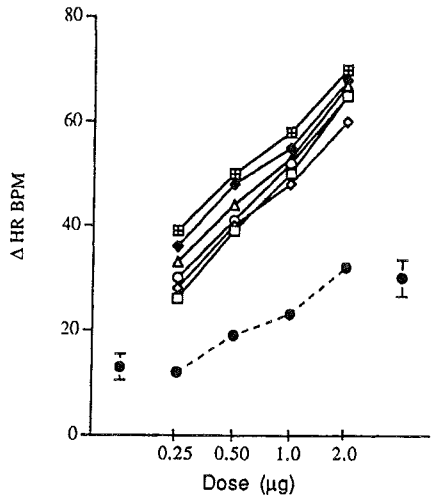

FIG 2. Isoproterenol dose-response curves for each patient are shown. Increased sensitivity to each individual dose was noted when compared with control subjects (broken line, n=15). BPM indicates beats per minute; HR, heart rate.

variability. Previous reports have established the reliability of this method in assessing the autonomic balance to the sinus node.[5-11] Sympathovagal balance, assessed by the LF/HF ratio both in the supine position and during upright tilt, was within normal ranges. These findings indicate that altered sympathovagal balance to the sinus node is not a major factor in the genesis of this tachycardia.

The sinus node response to β-adrenergic stimulation was markedly enhanced. Similarly, a markedly depressed cardiovagal response was noted in all patients. This finding suggests that the response to efferent vagal stimulation of the sinus node is impaired or that the integrity of the cardiovagal reflex is altered. The latter explanation appears to be unlikely given the fact that we observed normal sympathovagal balance both in the supine and upright positions, suggesting that the integrity of the baroreceptor reflex response is preserved. Impaired response of the sinus node to efferent vagal stimulation may enhance β-adrenergic sensitivity leading to increased sinus node response.

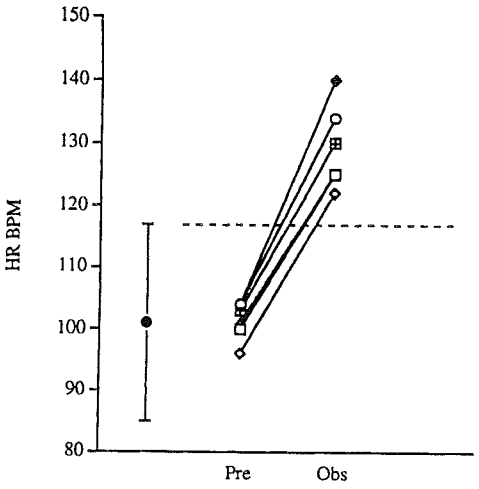

FIG 3. Line plot: Intrinsic heart rate. Predicted (Pre) and observed (Obs) intrinsic heart rates (HR) in each patient are shown. The predicted heart rate range and upper heart rate limit are indicated by the standard deviation (±2 SD) bar and dashed line, respectively, for all the patients. Intrinsic heart rate was increased in all patients. BPM indicates beats per minute.

A striking increase in IHR was observed in all patients. Heart rate in the pharmacologically denervated heart reflects the intrinsic sinus node rate.[17,18] This suggests that the mechanism leading to tachycardia in our patients was related to a primary sinus node abnormality resulting in a high IHR. Enhanced sinus node automaticity was potentiated by β-adrenergic hypersensitivity and impaired response to vagal stimulation.

Bauernfeind et al[1] described the effects of autonomic modulation in 7 patients with "idiopathic chronic sinus tachycardia." The mechanism of increased sinus node response was related to alterations in either sympathetic (2 patients) or vagal control of resting heart rate (5 patients) associated with abnormalities of IHR in some patients. These findings agree with our study. However, we were unable to demonstrate an alteration in resting control of heart rate. This disparity may be attributed to several alternative explanations. Bauernfeind's patients had a history of chronic sinus tachycardia with increased resting heart rate documented in all cases in contrast to only one patient in our series. The duration of symptoms was also distinctively different, with a mean duration of 6 years in Bauernfeind's series compared with 10 months in our series. Interestingly, the only patient of our series with increased resting heart rate reported a symptom duration of 3 years. It is therefore possible that the increased resting heart rate reported in Bauernfeind's series is related to the chronicity of symptoms, representing one end of the spectrum of IST. On the other hand, this discrepancy may be related to the method chosen to determine autonomic balance of heart rate at rest. Bauernfeind et al determined changes in heart rate to pharmacological interventions (atropine/propranolol), and this may not reflect sympathovagal balance to the sinus node.[19] Beat-to-beat variability of heart rate assessed by power spectral analysis provides an accurate estimate of the sympathovagal balance of the resting heart rate as well as during orthostatic stress.[5-11]

Schondorf and Low[20] and Fouad et al[21] have recently described a remarkably similar disorder predominantly observed in young women with otherwise normal hearts. Postural orthostatic tachycardia syndrome is characterized by a normal resting heart rate and exaggerated postural sinus tachycardia of 40 to 60 beats per minute elicited by upright tilt in the absence of orthostatic hypotension.[20,21] Increased β-adrenergic sensitivity comparable to that reported in this series has also been reported.[21] Similarly, respiratory sinus arrhythmia, which is an index of resting vagal efferent traffic, was normal in 16 patients with postural orthostatic hypotension.[20] The striking clinical and functional similarities shared between IST, postural orthostatic tachycardia, and chronic nonparoxysmal sinus tachycardia syndromes raise the possibility that these disorders represent the spectrum of a homogeneous disease process. However, the possibility that these syndromes represent a heterogeneous disorder cannot be ruled out.

Patients with IST are usually controlled by medical therapy with β-blockers. However, some may develop intolerable adverse effects or may be refractory to

medical therapy. Nonpharmacological therapy includes subtotal right atrial surgical exclusion.[4] More recently, mechanical or chemical occlusion of the sinus node artery has been reported.[22] Radiofrequency catheter ablation of the sinus node area was performed in one patient refractory to medical therapy. Junctional rhythm was observed for a period of 48 hours, and sinus rhythm was restored thereafter. This patient has remained free of symptoms despite recovering sinus rhythm. The explanation for this phenomenon is unclear. It is possible that ablation of a critical number of pacemaker cells involved in the development and maintenance of sinus tachycardia was achieved. Recovery of sinus rhythm after 48 hours of junctional rhythm may be due to resolution of edema induced by radiofrequency energy. Recently, modification of sinus node function by graded epicardial laser radiation has been reported in a dog model resembling IST.[23] Widespread distribution of the atrial pacemaker complex has been documented in dogs and humans.[24,25] It is possible that restoration of normal sinus rhythm in our case may be due to shifting of the atrial pacemaker complex to an alternate area in the vicinity of the sinus node.

Study Limitations

Electrophysiological studies were not performed in all patients. Nonetheless, all patients fulfilled the clinical criteria for IST, and electrophysiological study has not been shown to be helpful in elucidating the mechanism of this arrhythmia in previous studies.[1,4] Furthermore, the response to autonomic tests would be unlikely in subjects with sinus node reentry or atrial tachycardia. However, it is impossible to rule out the presence of an abnormal ectopic atrial focus in the vicinity of the sinus node.

These data suggest that the mechanism leading to IST is related to a primary sinus node abnormality resulting in high IHR, potentiated by a depressed cardiovagal reflex and β-adrenergic hypersensitivity.

Acknowledgments

This study was supported by the Heart and Stroke Foundation of Ontario, Toronto, Ontario, Canada. Dr Morillo is the recipient of a Research Fellowship Award from the Heart and Stroke Foundation of Canada. Dr Klein is the recipient of a Distinguished Research Professorship of the Heart and Stroke Foundation of Ontario, Toronto, Canada. Dr David Newman provided the follow-up data on the patient who underwent radiofrequency ablation.

References

1. Bauernfeind RA, Amat-Y-Leon F, Dhingra RC, Kehoe R, Wyndham C, Rosen KM. Chronic nonparoxysmal sinus tachycardia in otherwise healthy persons. *Ann Intern Med.* 1979;91: 702-710.
2. Codvelle MM, Boucher H. Tachycardie sinusale permanente a haute frequence sans troubles fonctionnels. *Bull Mem Soc Med Hop Paris.* 1939;54:1849-1852.
3. Wising P. Familial, congenital sinus tachycardia. *Acta Med Scand.* 1941;108:299-305.
4. Yee R, Guiraudon GM, Gardner MJ, Gulamhusein SS, Klein GJ. Refractory paroxysmal sinus tachycardia: management by subtotal right atrial exclusion. *J Am Coll Cardiol.* 1984;3:400-404.
5. Akselrod S, Gordon D, Ubel FA, Shannon DC, Barger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe beat-to-beat cardiovascular control. *Science.* 1981;213: 220-222.
6. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. *Circulation.* 1991;84:482-492.
7. Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, Sandrone G, Malfatto G, Dell'Orto S, Piccaluga E, Turiel M, Baselli G, Cerutti S, Malliani A. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympathovagal interaction in conscious man and dog. *Circ Res.* 1986; 59:178-193.
8. Fallen EL, Kamath MV, Ghista DN. Power spectrum of heart rate variability: a non-invasive test of integrated neurocardiac function. *Clin Invest Med.* 1988;2:331-340.
9. Pomeranz B, Macaulay RJB, Caudill MA, Kutz I, Adam D, Gordon D, Kilborn KA, Barger C, Shannon DC, Cohen RJ, Benson H. Assessment of autonomic function in humans by heart rate spectral analysis. *Am J Physiol.* 1985;248:H151-H153.
10. Vybiral T, Bryg RJ, Maddens ME, Boden WE. Effect of passive tilt on sympathetic and parasympathetic components of heart rate variability in normal subjects. *Am J Cardiol.* 1989;63:1117-1120.
11. Morillo CA, Klein GJ, Yee R, Jones DL, Odlum-Blair JK, Norris CI. Power spectral analysis of heart rate variability during passive tilt identifies patients with neurally mediated syncope. *Circulation.* 1992;86(suppl I):I-528. Abstract.
12. Khurana RK, Sdakiyo W, Hebel JR, Toro R, Erland N. Cold face test in the assessment of trigeminal-brainstem-vagal function in humans. *Ann Neurol.* 1980;7:144-149.
13. Heath ME, Downey JA. The cold face test (diving reflex) in clinical autonomic assessment: methodological considerations and repeatability of responses. *Clin Sci.* 1990;78:139-147.
14. Morillo CA, Echeverry D, Bohorquez R, Moreno P, Jaramillo M, Diaz A, Gonzalez ND. Evaluación de la función autonómica por un método no invasivo en personas asintomáticas. *Acta Med Colomb.* 1990;15(suppl):227. Abstract.
15. Moreno PR, Morillo CA, Diaz A, Buitrago T, Echeverri D. Evaluación de la función autonómica en pacientes post-infarto. *Acta Med Colomb.* 1990;15(suppl):227. Abstract.
16. Cleaveland CR, Rangno RE, Shand DG. A standardized isoproterenol sensitivity test. *Arch Intern Med.* 1972;130:47-52.
17. Jose AD. Effect of combined sympathetic and parasympathetic blockade on heart rate and cardiac function in man. *Am J Cardiol.* 1966;18:476-478.
18. Jose AD, Collison D. The normal range and determinants of the intrinsic heart rate in man. *Cardiovasc Res.* 1970;4:160-167.
19. Ewing DJ. Practical bedside investigation of diabetic autonomic failure. In: Bannister R, ed. *Autonomic Failure. A Textbook of Clinical Disorders of the Autonomic Nervous System.* Oxford: Oxford University Press; 1983:371-405.
20. Schondorf R, Low PA. Idiopathic postural tachycardia syndromes. In: Low PA, ed. *Clinical Autonomic Disorders.* Boston: Little, Brown, Co; 1993:641-652.
21. Fouad FM, Tadena-Thome L, Bravo EL, Tarazi R. Idiopathic hypovolemia. *Ann Intern Med.* 1986;104:298-303.
22. De Paola AAV, Horowitz LN, Vattimo AC, Marques FBR, Miyamoto MH, Terzian AB, Cirenza C, DeSouza IA, Portugal OP, Martinez-Fo EE. Sinus node artery occlusion for treatment of chronic nonparoxysmal sinus tachycardia. *Am J Cardiol.* 1992;70: 128-130.
23. Littman L, Svenson RH, Gallagher JJ, Bharati S, Lev M, Linder KD, Tatsis GP, Nichelson C. Modification of sinus node function by epicardial laser irradiation in dogs. *Circulation.* 1990;81:350-359.
24. Boineau JP, Schuessler RB, Hackel DB, Miller CB, Brockus CW, Wylds AC. Widespread distribution and rate differentiation of atrial pacemaker complex. *Am J Physiol.* 1980;239:H406-H415.
25. Boineau JP, Canavan TE, Schuessler RB, Cain ME, Corr PB, Cox JL. Demonstration of a widely distributed atrial pacemaker complex in the human heart. *Circulation.* 1988;77:1221-1237.