Hyperadrenergic Postural Tachycardia Syndrome in Mast Cell Activation Disorders

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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.

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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.

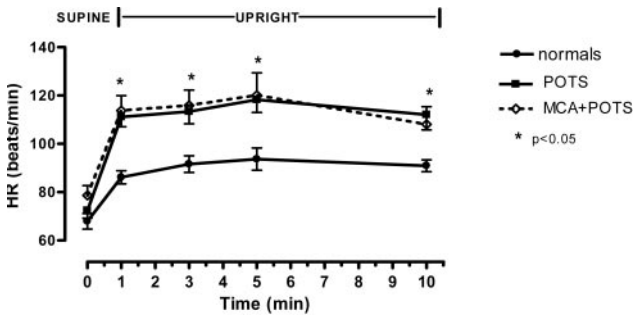

Figure 1. Dynamic change in heart rate (HR) induced by upright posture in normal subjects and patients with POTS and MCA+POTS. There was a significant difference in HR between both groups of patients and normal controls ($P<0.05$) already evident by the first minute of upright posture. There was no difference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

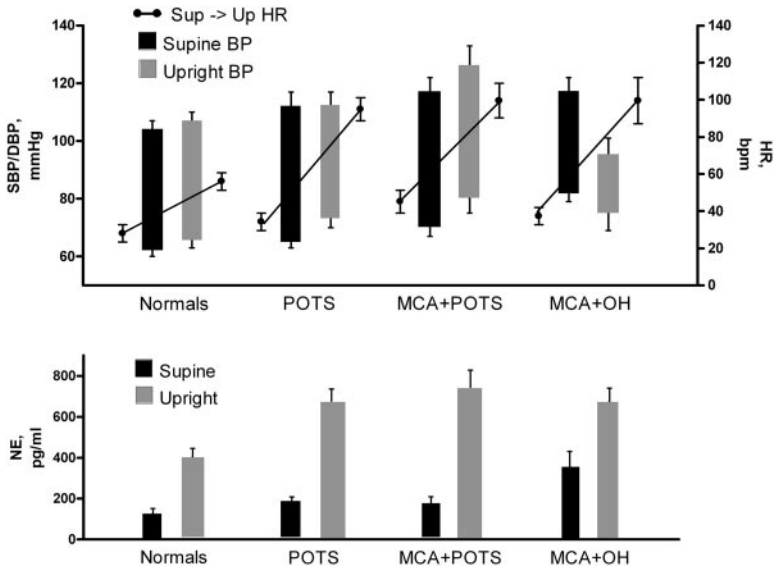

Figure 2. Hemodynamic and humoral effect of posture in normal subjects and patients with POTS, MCA+POTS, and MCA+OH. Top, Postural change in heart rate (HR; ●) and systolic/diastolic blood pressure (floating bars). Bottom, Supine and upright plasma norepinephrine (NE) taken from an antecubital vein.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

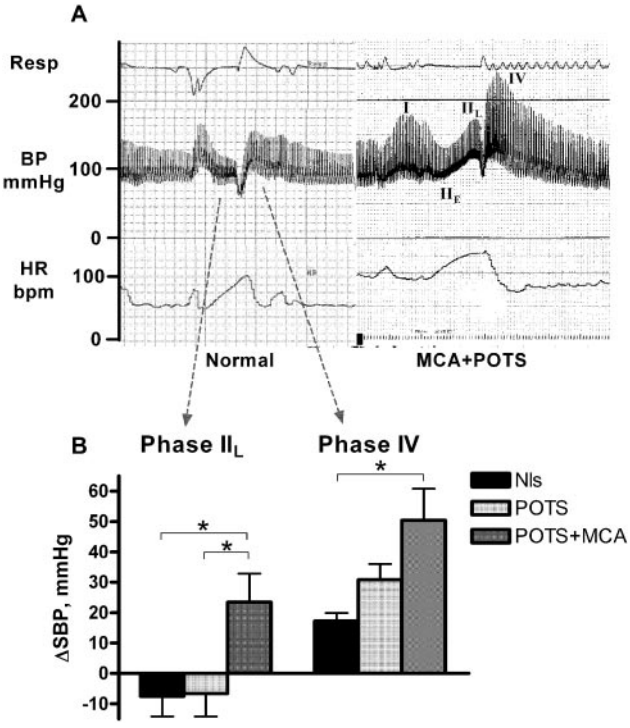

Figure 3. Cardiovascular response to the Valsalva maneuver in normal controls (NIs), patients with POTS, and patients with MCA+POTS. A, Comparison of representative tracings of a normal control and a patient with MCA+POTS showing the exaggerated increase in blood pressure during phase II_{Late} and phase 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.

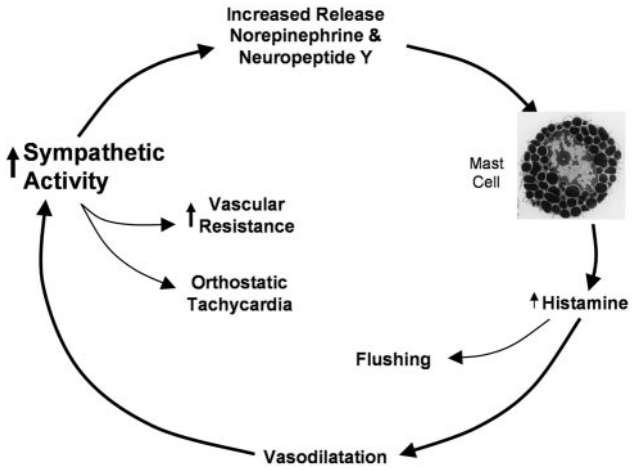

Figure 4. Proposed pathophysiological mechanisms underlying the association between MCA and hyperadrenergic orthostatic intolerance. See Discussion.

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

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