

THE NEUROPATHIC POSTURAL TACHYCARDIA SYNDROME

GIRIS JACOB, M.D., D.Sc., FERNANDO COSTA, M.D., JOHN R. SHANNON, M.D., ROSE MARIE ROBERTSON, M.D., MARK WATHEN, M.D., MICHAEL STEIN, M.D., ITALO BIAGGIONI, M.D., ANDY ERTL, Ph.D., BONNIE BLACK, R.N., AND DAVID ROBERTSON, M.D.

ABSTRACT

Background The postural tachycardia syndrome is a common disorder that is characterized by chronic orthostatic symptoms and a dramatic increase in heart rate on standing, but that does not involve orthostatic hypotension. Several lines of evidence indicate that this disorder may result from sympathetic denervation of the legs.

Methods We measured norepinephrine spillover (the rate of entry of norepinephrine into the venous circulation) in the arms and legs both before and in response to exposure to three stimuli (the cold pressor test, sodium nitroprusside infusion, and tyramine infusion) in 10 patients with the postural tachycardia syndrome and in 8 age- and sex-matched normal subjects.

Results At base line, the mean (\pm SD) plasma norepinephrine concentration in the femoral vein was lower in the patients with the postural tachycardia syndrome than in the normal subjects (135 ± 30 vs. 215 ± 55 pg per milliliter [0.80 ± 0.18 vs. 1.27 ± 0.32 nmol per liter], $P=0.001$). Norepinephrine spillover in the arms increased to a similar extent in the two groups in response to each of the three stimuli, but the increases in the legs were smaller in the patients with the postural tachycardia syndrome than in the normal subjects (0.001 ± 0.09 vs. 0.12 ± 0.12 ng per minute per deciliter of tissue [0.006 ± 0.53 vs. 0.71 ± 0.71 nmol per minute per deciliter] with the cold pressor test, $P=0.02$; 0.02 ± 0.07 vs. 0.23 ± 0.17 ng per minute per deciliter [0.12 ± 0.41 vs. 1.36 ± 1.00 nmol per minute per deciliter] with nitroprusside infusion, $P=0.01$; and 0.008 ± 0.09 vs. 0.19 ± 0.25 ng per minute per deciliter [0.05 ± 0.53 vs. 1.12 ± 1.47 nmol per minute per deciliter] with tyramine infusion, $P=0.04$).

Conclusions The neuropathic postural tachycardia syndrome results from partial sympathetic denervation, especially in the legs. (N Engl J Med 2000;343:1008-14.)

©2000, Massachusetts Medical Society.

THE postural tachycardia syndrome is a chronic form of orthostatic intolerance that primarily affects young women. This disorder is characterized by symptoms (such as lightheadedness, dimming of vision, confusion, and anxiety) and signs (such as bluish-red skin in dependent limbs) that occur on standing and that are relieved by lying down or sitting.^{1,2} A remarkable physical finding is a dramatic increase in the heart rate that oc-

curs on standing and that is not associated with a decrease in blood pressure.³ Patients with this syndrome frequently have high plasma catecholamine concentrations, a finding that suggests that the disorder is a primary hyperadrenergic condition.^{1,4-7} The syndrome, which has also been referred to as idiopathic orthostatic intolerance,⁸⁻¹¹ has features in common with the mitral-valve prolapse syndrome,¹² the hyperdynamic β -adrenergic circulatory state,¹³ and vasoregulatory asthenia.¹

Patients with the postural tachycardia syndrome often have high plasma norepinephrine concentrations,¹⁴ hypovolemia,^{4,15} excessive pooling of the blood in the legs while standing,¹⁶ and exaggerated orthostatic hypovolemia.^{3,17,18} These findings help explain some of the clinical features of the disorder, but few studies have examined its pathophysiology. Several lines of evidence indicate that sympathetic denervation of the legs may be the underlying mechanism. The results of galvanic skin testing^{19,20} and quantitative testing of the sudomotor axon reflex suggest that autonomic denervation of the skin is present.^{21,22} The finding of hypersensitivity to infusion of norepinephrine into veins of the foot, despite high plasma catecholamine concentrations, suggests that denervation hypersensitivity of the veins of the legs is involved.¹⁸ Increased sensitivity to systemically administered phenylephrine and isoproterenol and resistance to the norepinephrine-releasing effects of tyramine⁹ are findings consistent with noradrenergic neuronal dysfunction, as is the short-term improvement in orthostatic symptoms after the administration of the α_1 -adrenergic-receptor agonist midodrine.⁸

To test the hypothesis that the postural tachycardia syndrome is caused by partial dysautonomia resulting in dysregulation of autonomic control of the cardiovascular system, we measured the spillover of norepinephrine (the rate of entry of norepinephrine into the venous circulation) in the arms and legs of patients with the postural tachycardia syndrome and in the arms and legs of normal subjects before and after exposure to several stimulators of sympathetic activation.

From the Jacob Recanati Autonomic Dysfunction Center and the Department of Internal Medicine C, Rambam Medical Center, Haifa, Israel (G.J.); and the Autonomic Dysfunction Center and the Departments of Medicine (E.C., J.R.S., R.M.R., M.W., M.S., I.B., A.E., B.B., D.R.), Pharmacology (D.R.), and Neurology (D.R.), Vanderbilt University, Nashville. Address reprint requests to Dr. David Robertson at the Autonomic Dysfunction Center, AA3228 MCN, Vanderbilt University, Nashville, TN 37232-2195, or at david.robertson@memail.vanderbilt.edu.

METHODS

Study Population

Between February 1995 and September 1996, we studied 18 patients (16 women and 2 men) who had been referred to the Autonomic Dysfunction Center at Vanderbilt University (Nashville) for the evaluation and treatment of debilitating symptoms consistent with the postural tachycardia syndrome. Most of these patients underwent extensive testing, some of the results of which have been reported previously.^{8,9} Patients with systemic illnesses that might affect the autonomic nervous system were excluded.

All potentially eligible patients underwent a physical examination and were interviewed with use of a questionnaire to determine the type and extent of their symptoms. Patients were enrolled if they met the following criteria: an increase in the heart rate of at least 30 beats per minute (without a concomitant decrease in systolic blood pressure of more than 20 mm Hg or in diastolic pressure of more than 10 mm Hg) within five minutes after assuming a standing position on at least three separate occasions; a plasma norepinephrine concentration of at least 600 pg per milliliter (3.5 nmol per liter) on standing; and the presence of characteristic symptoms of the postural tachycardia syndrome for at least six months. The last 10 patients enrolled also underwent testing to assess norepinephrine spillover. We also studied 10 normal subjects (8 women and 2 men) matched for age and sex with the patients; 8 of the 10 normal subjects underwent norepinephrine-spillover testing. All the investigational procedures were approved by the Vanderbilt University institutional review board, and all the patients and normal subjects gave written informed consent before entering the study.

Experimental Design

All the patients and normal subjects were admitted to the General Clinical Research Center at Vanderbilt University and given a diet that contained 150 mmol of sodium and 70 mmol of potassium per day, no caffeine, and low levels of monoamines. All current medications were discontinued at least two weeks before admission, and smoking was not permitted during the study. After three days of this diet and an overnight rest in the supine position, blood was obtained for blood-volume measurements. Blood pressure, heart rate, and plasma catecholamine concentrations were measured with the subjects in the supine and upright positions. Blood volume was measured by a modification¹⁵ of the technique of Campbell et al.²³ Plasma catecholamine concentrations were measured by high-performance liquid chromatography with electrochemical detection.²⁴ Testing of autonomic function (the change in the heart rate in response to controlled ventilation and in response to hyperventilation, the change in the heart rate in response to the Valsalva maneuver, and the change in blood pressure in response to sustained handgrip exercise) was performed as previously described.²⁵

On the following day, sympathetic-nerve function was tested (in 10 of the patients and in 8 of the normal subjects) by measuring the rate of entry of norepinephrine into the systemic circulation (systemic spillover) or into the local venous drainage (local spillover). Subjects were studied after an overnight rest in the supine position and an overnight fast. After catheterization of the brachial artery (for blood-pressure monitoring and blood sampling), the ipsilateral femoral vein (for blood sampling), and two large antecubital veins (one ipsilateral to the arterial line for blood sampling and one contralateral to the arterial catheter for the infusion of tritiated norepinephrine), the subjects rested for 30 minutes. Tritiated norepinephrine (sterile, pyrogen-free levo-[ring-2,5,6-³H]-norepinephrine [Dupont—New England Nuclear, Boston]) was then administered intravenously, first as a 25- μ Ci loading dose over a two-minute period and then at an infusion rate of 0.9 μ Ci per milliliter per minute.⁹ After 30 minutes, when a steady state had been attained, blood samples for the measurement of norepinephrine spillover were simultaneously obtained from the brachial artery, the femoral vein, and an antecubital vein. Blood flow in

a forearm and leg was then measured by venous-occlusion air plethysmography.^{26,27}

Norepinephrine spillover and other variables were measured during stimulation by three methods: immersion of the contralateral hand in ice water for at least one minute (the cold pressor test), infusion of sodium nitroprusside (at an initial rate of 0.1 μ g per kilogram of body weight per minute in the arm contralateral to that in which blood flow was measured, with the rate increased until systolic blood pressure had decreased by approximately 20 mm Hg), and infusion of tyramine (0.25 mg per minute until systolic blood pressure had increased by approximately 25 mm Hg). Values for norepinephrine spillover were determined before and during exposure to each of these stimuli, and at least 20 minutes was allowed after each stimulus for recovery. The concentrations of ³H-norepinephrine in plasma were measured as previously described.⁹

Determination of Norepinephrine Kinetics

Norepinephrine kinetics were calculated by the one-compartment model of Esler et al.²⁸ Systemic norepinephrine clearance (in liters per minute) was defined as the rate of infusion of [³H]norepinephrine (in disintegrations per minute [dpm]) divided by the arterial concentration of [³H]norepinephrine (in dpm per liter). Systemic norepinephrine spillover (in nanograms per minute) was calculated as systemic norepinephrine clearance multiplied by the arterial plasma concentration of norepinephrine (in nanograms per liter). The fractional extraction of [³H]norepinephrine (a unitless measure) in the arm or leg was calculated as $(A^* - V^*) / A^*$, where A^* and V^* are the arterial and venous concentrations of [³H]norepinephrine (in dpm per liter), respectively. Local norepinephrine spillover (in nanograms per minute per deciliter of tissue) in the arm or leg was calculated as $([V - A] + A[EF]) \times PF$, where V is the local venous plasma norepinephrine concentration (in nanograms per liter), A the arterial norepinephrine concentration (in nanograms per liter), EF the fractional extraction of norepinephrine, and PF the local plasma flow (calculated as the blood flow \times $[1 - \text{hematocrit}]$, expressed in milliliters per minute per deciliter of tissue). Local norepinephrine clearance (in liters per minute) was calculated as $EF \times PF$. The term "spillover" is used, rather than "release," because what was measured was not the norepinephrine released from the sympathetic neurons but, more accurately, the norepinephrine that escaped from the synaptic and neuronal pools into the circulation.

Statistical Analysis

The results are expressed as means \pm SD. Paired and unpaired *t*-tests were used for comparisons between groups and within each group before and after exposure to the various stimuli. One-way analysis of variance for repeated measures was used to assess the effect of time on each of the variables. Data were analyzed with Quattro Pro software, version 7 (Corel, Jericho, N.Y.) and GraphPad Prism software, version 2.0 (GraphPad Software, San Diego, Calif.). All *P* values are two-sided.

RESULTS

Characteristics of the Study Population

The blood pressure in the supine and upright positions and the heart rate in the supine position were similar in the patients with the postural tachycardia syndrome and the normal subjects (Table 1). The mean heart rate in the upright position was 113 ± 13 beats per minute in the patients and 82 ± 7 beats per minute in the normal subjects. In the supine position, the mean plasma norepinephrine and epinephrine concentrations were similar in the two groups, but in the upright position, the plasma norepineph-

TABLE 1. CHARACTERISTICS OF THE PATIENTS WITH THE POSTURAL TACHYCARDIA SYNDROME AND THE NORMAL SUBJECTS.*

VARIABLE	PATIENTS (N=18)	NORMAL SUBJECTS (N=10)	P VALUE†
Age — yr	34±8	33±7	1.00
Weight — kg	64±8	64±7	1.00
Height — cm	166±8	167±9	0.76
Total blood volume — liters	3.7±0.5	4.1±0.7	0.06
Heart rate — beats/min			
Supine	72±12	66±9	0.18
Upright	113±13	82±7	<0.001
Blood pressure — mm Hg			
Systolic			
Supine	117±17	108±10	0.10
Upright	112±20	106±13	0.40
Diastolic			
Supine	67±13	63±10	0.42
Upright	77±17	72±6	0.38
Plasma norepinephrine — pg/ml			
Supine	210±85	220±95	0.77
Upright	840±500	430±80	0.02
Plasma epinephrine — pg/ml			
Supine	37±22	31±22	0.55
Upright	80±42	47±30	0.04
Orthostatic symptoms — no. (%)‡			
Lightheadedness or dizziness	18 (100)		
Exercise intolerance	15 (83)		
Fatigue	12 (67)		
Blurred vision	11 (61)		
Chest discomfort	11 (61)		
Palpitation	7 (39)		
Clamminess	10 (56)		
Anxiety	10 (56)		
Syncope	10 (56)		
Nausea (while standing)	9 (50)		
Tremulousness	9 (50)		
Flushing (particularly after meals)	8 (44)		
Headache (while standing)	8 (44)		
Associated findings — no. (%)			
Mitral-valve prolapse	9 (50)		
Irritable bowel syndrome	4 (22)		
Chronic fatigue syndrome	3 (17)		
Inflammatory bowel disease	3 (17)		

*Plus-minus values are means ±SD. To convert the values for norepinephrine to nanomoles per liter, multiply by 0.0059. To convert the values for epinephrine to nanomoles per liter, multiply by 0.0055.

†P values were calculated by the unpaired two-tailed t-test.

‡The normal subjects did not report any symptoms.

rine concentration was substantially higher in the patients than in the normal subjects (840 ± 500 vs. 430 ± 80 pg per milliliter [5.0 ± 3.0 vs. 2.5 ± 0.5 nmol per liter], $P=0.02$), as was the plasma epinephrine concentration (80 ± 42 vs. 47 ± 30 pg per milliliter [0.44 ± 0.23 vs. 0.26 ± 0.16 nmol per liter], $P=0.04$). Lightheadedness or dizziness and exercise intolerance were the symptoms most frequently reported by the patients (Table 1). Most of the patients could not precisely identify the point in time at which their symptoms had begun, but the mean estimated time of onset was about 2.5 years (range, 8 months to 7 years) before the beginning of the study.

The autonomic-function tests revealed normal parasympathetic control of the heart rate in both the patients and the normal subjects (sinus arrhythmia ratio, 1.5 ± 0.2 and 1.4 ± 0.1 , respectively; Valsalva ratio, 2.0 ± 0.3 and 1.9 ± 0.4 , respectively). The increase in blood pressure during sustained handgrip exercise was higher in the patients than in the normal subjects (15 ± 7 vs. 9 ± 5 mm Hg, $P=0.02$). The increase in heart rate with hyperventilation was also greater in the patients than in the normal subjects (21 ± 5 vs. 4 ± 1 beats per minute, $P=0.01$).

Local and Systemic Spillover and Clearance of Norepinephrine

Local and systemic norepinephrine spillover was measured in 10 of the 18 patients (8 women and 2 men) and in 8 of the 10 normal subjects (6 women and 2 men). At base line, the mean norepinephrine concentration in the femoral vein was significantly lower in the patients than in the normal subjects (Table 2). Systolic blood pressure increased by a similar amount in the two groups during the cold pressor test and decreased by a similar amount during nitroprusside infusion. During nitroprusside infusion, the heart rate increased in both groups, but the increase was greater in the patients than in the normal subjects (27 ± 6 vs. 12 ± 5 beats per minute, $P<0.001$).

There was no effect of time on any of the measured or calculated values (i.e., no significant change in base-line values). The fractional extraction of [^3H]-norepinephrine before exposure to each of the three stimuli was similar in the patients and the normal subjects, both in the arms (55 ± 13 and 56 ± 14 percent in the two groups, respectively) and in the legs (56 ± 10 and 55 ± 9 percent, respectively).

Norepinephrine spillover before exposure to each of the three stimuli was lower in the patients than in the normal subjects, both in the arms and in the legs (Fig. 1). In the arms, before exposure to each of the stimuli, norepinephrine clearance was similar in the two groups, but in the legs it was lower in the patients than in the normal subjects (Fig. 2). During exposure to each of the three stimuli, norepinephrine spillover in the arms increased by a similar amount in the two groups, but in the legs the increases were significantly smaller in the patients than in the normal subjects (0.001 ± 0.09 vs. 0.12 ± 0.12 ng per minute per deciliter [0.006 ± 0.53 vs. 0.71 ± 0.71 nmol per minute per deciliter] with the cold pressor test, $P=0.02$; 0.02 ± 0.07 vs. 0.23 ± 0.17 ng per minute per deciliter [0.12 ± 0.41 vs. 1.36 ± 1.00 nmol per minute per deciliter] with nitroprusside infusion, $P=0.01$; and 0.008 ± 0.09 vs. 0.19 ± 0.25 ng per minute per deciliter [0.05 ± 0.53 vs. 1.12 ± 1.47 nmol per minute per deciliter] with tyramine infusion, $P=0.04$) (Fig. 3). The increase in norepinephrine clearance in the arms was similar in the patients and the normal subjects, but in the legs the norepinephrine clearance

THE NEUROPATHIC POSTURAL TACHYCARDIA SYNDROME

TABLE 2. EFFECTS OF EXPOSURE TO THREE STIMULI OF THE SYMPATHETIC NERVOUS SYSTEM IN 10 PATIENTS WITH THE POSTURAL TACHYCARDIA SYNDROME AND 8 NORMAL SUBJECTS.*

VARIABLE	COLD PRESSOR TEST			NITROPRUSSIDE†			TYRAMINE‡		
	PATIENTS	NORMAL SUBJECTS	P VALUE§	PATIENTS	NORMAL SUBJECTS	P VALUE§	PATIENTS	NORMAL SUBJECTS	P VALUE§
Blood pressure (mm Hg)									
Systolic									
Before stimulus	112±13	108±6	0.43	105±13	107±6	0.69	108±10	106±3	0.60
During stimulus	135±15	125±9	0.12	95±15	87±6	0.18	135±7	133±6	0.53
P value¶	0.01	0.005	—	<0.001	<0.001	—	<0.001	<0.001	—
Change	23±13	18±39	0.70	-20±5	-19±3	0.65	27±4	27±5	1.00
Mean									
Before stimulus	69±6	69±3	1.00	72±6	67±3	0.05	68±7	65±3	0.28
During stimulus	85±9	81±11	0.40	61±9	58±6	0.43	88±7	77±6	0.03
P value¶	<0.001	0.01	—	<0.001	<0.001	—	<0.001	<0.001	—
Heart rate (beats/min)									
Before stimulus	73±10	66±11	0.18	71±9	67±11	0.40	70±9	66±11	0.41
During stimulus	82±12	71±14	0.09	98±12	80±11	0.005	73±9	63±9	0.04
P value¶	0.005	0.06	—	<0.001	0.01	—	0.80	0.45	—
Blood flow (ml/min/dl)									
Forearm									
Before stimulus	3.9±1.3	4.1±1.4	0.76	3.8±1.3	4.3±1.4	0.45	3.9±1.9	3.9±1.4	0.90
During stimulus	4.2±1.9	4.2±1.1	1.00	4.0±1.3	4.9±1.7	0.22	6.9±2.5	6.7±2.8	0.87
P value¶	0.55	0.83	—	0.52	0.13	—	<0.001	0.01	—
Leg									
Before stimulus	2.4±0.9	3.6±1.4	0.04	2.4±0.9	3.5±1.7	0.08	2.3±0.7	3.7±1.4	0.02
During stimulus	2.7±1.3	4.6±2.2	0.035	2.6±0.9	4.1±2.3	0.07	3.4±1.6	5.4±2.3	0.05
P value¶	0.12	0.02	—	0.06	0.15	—	0.04	0.01	—
Plasma norepinephrine (pg/ml)									
Arterial									
Before stimulus	165±45	215±30	0.02	175±60	205±45	0.26	185±80	235±28	0.11
During stimulus	250±60	250±30	1.00	353±100	335±85	0.70	320±80	375±65	0.14
P value¶	0.002	0.02	—	<0.001	0.003	—	0.01	<0.001	—
Antecubital venous									
Before stimulus	180±60	240±55	0.04	205±60	245±55	0.16	195±60	260±28	0.01
During stimulus	260±60	346±55	0.01	355±90	340±55	0.68	275±80	335±85	0.14
P value¶	0.05	0.02	—	<0.001	<0.001	—	0.02	0.05	—
Femoral venous									
Before stimulus	135±30	215±55	0.001	175±60	245±70	0.03	160±50	225±42	<0.01
During stimulus	205±50	250±45	0.06	300±100	370±45	0.08	210±60	335±110	0.007
P value¶	0.01	0.04	—	<0.001	0.003	—	0.02	0.04	—
Systemic arterial norepinephrine spillover (ng/min)									
Before stimulus	340±180	505±168	0.06	360±220	510±250	0.19	450±350	500±110	0.70
During stimulus	600±220	670±285	0.55	840±320	745±195	0.45	770±430	790±140	0.90
P value¶	0.003	0.003	—	<0.001	0.07	—	<0.001	<0.001	—
Systemic arterial norepinephrine clearance (liters/min)									
Before stimulus	2.0±1.8	2.2±0.8	0.78	2.0±1.9	2.4±0.6	0.57	2.3±1.0	2.1±0.5	0.62
During stimulus	2.4±1.0	2.6±0.9	0.66	2.4±0.9	2.3±0.6	0.79	2.5±0.9	2.1±0.3	0.25
P value¶	0.04	0.09	—	0.08	0.70	—	0.49	1.00	—

*Plus-minus values are means ±SD. To convert the values for norepinephrine to nanomoles per liter, multiply by 0.0059.

†The patients received a mean dose of 1.1±0.3 µg per kilogram, and the normal subjects a mean dose of 1.0±0.2 µg per kilogram (P=0.25).

‡The patients received a mean dose of 1.8±0.4 mg, and the normal subjects a mean dose of 1.3±0.3 mg (P=0.04).

§P values are for the comparison between the patients and the normal subjects and were calculated by the unpaired two-tailed t-test.

¶P values are for the comparison between the values before and after stimulation and were calculated by the paired two-tailed t-test.

||Blood flow was expressed in milliliters per minute per deciliter of tissue.

tended to increase less in the patients than in the normal subjects (data not shown). During cold pressor testing and nitroprusside infusion, the fractional extraction of norepinephrine in the legs did not change significantly in either group. With tyramine infusion, the fractional extraction of norepinephrine decreased to 46±3 percent in the normal subjects but did not change in the patients (P=0.04).

DISCUSSION

The postural tachycardia syndrome is characterized by orthostatic symptoms and tachycardia without orthostatic hypotension. The nonspecific nature of the symptoms and the absence of orthostatic hypotension have probably resulted in a lack of recognition of this syndrome by both clinicians and investigators. Poorly defined diagnostic criteria and the

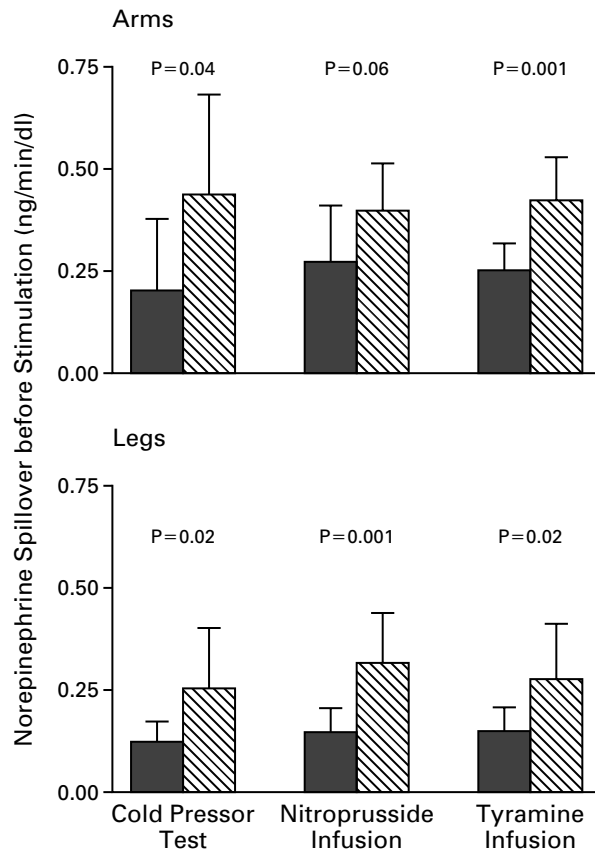


Figure 1. Mean (+SD) Norepinephrine Spillover in the Arms and Legs in 10 Patients with the Postural Tachycardia Syndrome (Solid Bars) and 8 Normal Subjects (Hatched Bars) before the Cold Pressor Test, Nitroprusside Infusion, and Tyramine Infusion.

P values were calculated by the unpaired two-tailed t-test. To convert the values for norepinephrine spillover to nanomoles per minute per deciliter, multiply by 5.9.

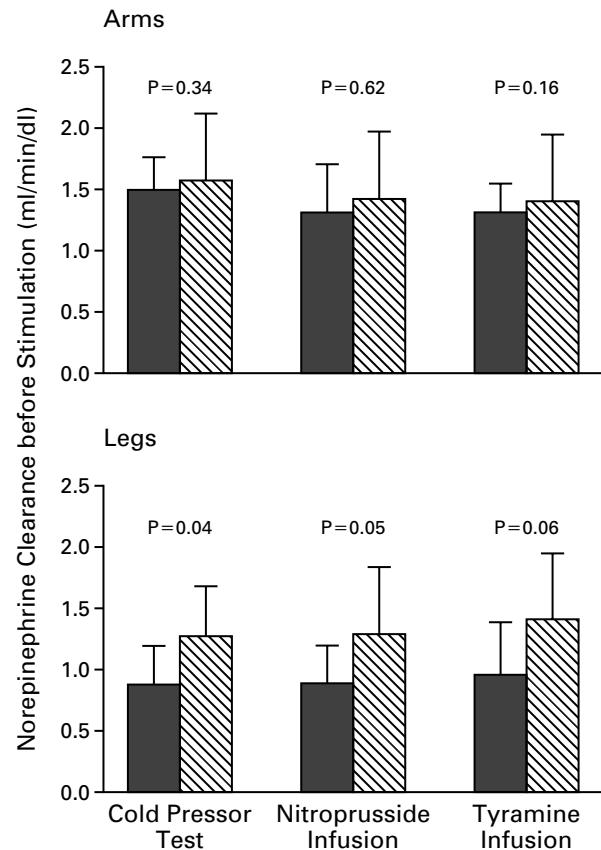


Figure 2. Mean (+SD) Norepinephrine Clearance in the Arms and Legs in 10 Patients with the Postural Tachycardia Syndrome (Solid Bars) and 8 Normal Subjects (Hatched Bars) before the Cold Pressor Test, Nitroprusside Infusion, and Tyramine Infusion.

P values were calculated by the unpaired two-tailed t-test.

likelihood of multiple causes have made it difficult to clarify the underlying pathophysiology. In the current study, we used stringent criteria to obtain as homogeneous a study group as possible. Only patients with an increase in the heart rate of at least 30 beats per minute on standing and a plasma norepinephrine concentration of at least 600 pg per milliliter on standing were included in the study.

Several previous investigations have provided clues that patients with the postural tachycardia syndrome have peripheral autonomic dysfunction. Streeten et al. found that patients with orthostatic tachycardia had excessive venous pooling in the legs while standing and suggested that denervation of the legs was a mechanism of the syndrome.¹⁶ This hypothesis was supported by the finding of hypersensitivity to infusion of norepinephrine into the veins of the foot, despite high plasma catecholamine concentrations.¹⁸ Other

investigators studying patients with a similar syndrome observed prolonged latency of plantar autonomic surface potentials during galvanic skin testing,^{19,20} as well as greater impairment of sweating in the legs than in the arms.²¹ Previously, we found that patients with the postural tachycardia syndrome were twice as sensitive as normal subjects to the hypertensive effect of the α_1 -adrenergic-receptor agonist phenylephrine⁹ and had short-term improvement in orthostatic tachycardia and orthostatic symptoms with the administration of the oral α_1 -adrenergic-receptor agonist midodrine⁸; these findings suggest that dysfunction of the peripheral autonomic neurons of the cardiovascular system may contribute to the pathophysiology of the postural tachycardia syndrome. Dysfunction of these nerves, if present, should become apparent when they are activated.

In the current study, we measured the responses

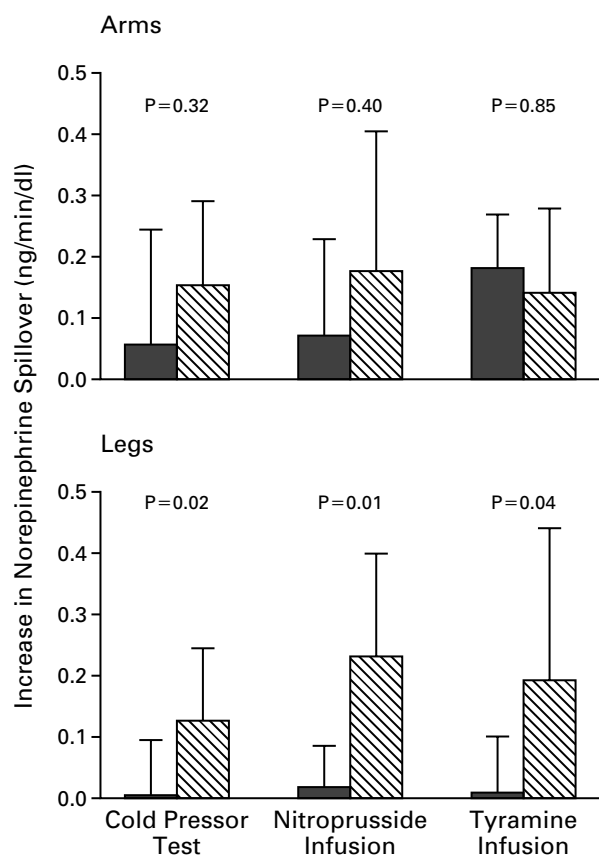


Figure 3. Mean (+SD) Increase in Norepinephrine Spillover in the Arms and Legs in 10 Patients with the Postural Tachycardia Syndrome (Solid Bars) and 8 Normal Subjects (Hatched Bars) during the Cold Pressor Test, Nitroprusside Infusion, and Tyramine Infusion.

P values were calculated by the unpaired two-tailed t-test. To convert the values for norepinephrine spillover to nanomoles per minute per deciliter, multiply by 5.9.

to three distinct stimuli of the sympathetic nervous system. The cold pressor test — a nonspecific, painful stimulus — activates the sympathetic nervous system centrally, increasing blood pressure and muscle sympathetic-nerve activity.²⁹ Nitroprusside induces hypotension, which in turn causes baroreflex-mediated increases in plasma catecholamine concentrations and muscle sympathetic-nerve activity.³⁰ Tyramine is taken up into the sympathetic neurons and causes the release of norepinephrine.^{31,32} These stimuli, each of which causes sympathetic activation by a different mechanism, increased norepinephrine spillover in the arms of both the patients with the postural tachycardia syndrome and the normal subjects, with similar increases in the two groups, but failed to increase norepinephrine spillover in the legs of the patients. Moreover, approximately 35 percent more tyramine was required in the patients than in the normal subjects to achieve similar pressor responses. These find-

ings suggest that in the legs of patients with the postural tachycardia syndrome, neuronal stores of norepinephrine are low, norepinephrine release is impaired, or the uptake of tyramine is impaired.³³ The results of the current study support the hypothesis that partial autonomic dysfunction that is more pronounced in the legs than in the arms can cause the postural tachycardia syndrome.

In the absence of stimulation, systemic norepinephrine spillover in these patients was normal despite the impaired spillover in the legs. This finding may be explained by the activation of intact sympathetic neurons in other organs (such as the mesentery), a process that contributes more than one third of the systemic spillover in normal subjects.³⁴ The reduced clearance of norepinephrine in the legs, without a similar reduction in the arms, may result from impairment of norepinephrine-reuptake mechanisms due to isolated damage to nerve terminals in the legs. Hypovolemia, shown previously to be present in patients with this syndrome,⁴ may result in a reduction in local blood flow and a subsequent reduction in norepinephrine spillover.³⁵ Changes in capillary permeability in the limbs,³⁶ the possibility of which is not addressed by assessments of spillover, may also contribute to the observed alterations in norepinephrine spillover and clearance. However, our data strongly implicate impaired noradrenergic function in the legs as the cause of a neuropathic form of the postural tachycardia syndrome.

The dysautonomia associated with the neuropathic postural tachycardia syndrome suggests that its treatment should be similar to that of pure autonomic failure, which results from nearly complete peripheral autonomic neuropathy.^{37,38} Autonomic failure is treated by increasing blood volume through greater intake of fluids and salt and administration of the mineralocorticoid agonist fludrocortisone³⁹ and by minimizing orthostatic pooling of the blood in the lower body with compression garments to increase extravascular hydrostatic pressure⁴⁰ or with short-acting vasoconstrictors to increase intravascular pressure.⁴¹⁻⁴³ Indeed, volume loading,⁸ administration of an α_1 -adrenergic-receptor agonist,⁸ and compression of the legs¹⁶ in patients with the postural tachycardia syndrome have been shown to decrease the severity of orthostatic tachycardia. Regular exercise, by increasing intravascular volume,⁴⁴ would probably also be beneficial. However, the long-term effects of these measures have not been determined.

Supported in part by grants (HL-56693 and RR-00095) from the National Institutes of Health, by a grant (NAS 9-19483) from the National Aeronautics and Space Administration, and by the Nathan Blaser Shy-Drager Research Program of Vanderbilt University.

REFERENCES

1. Wooley CF. Where are the diseases of yesteryear? DaCosta's syndrome, soldiers heart, the effort syndrome, neurocirculatory asthenia — and the mitral valve prolapse syndrome. *Circulation* 1976;53:749-51.

2. Low PA, Opfer-Gehrking TL, Textor SC, et al. Postural tachycardia syndrome (POTS). *Neurology* 1995;45:Suppl 5:S19-S25.
3. Jacob G, Ertl AC, Shannon JR, Robertson RM, Robertson D. Idiopathic orthostatic tachycardia: the role of dynamic orthostatic hypovolemia and norepinephrine. *Circulation* 1996;94:Suppl I:I-627. abstract.
4. Fouad FM, Tadana-Thome L, Bravo EL, Tarazi RC. Idiopathic hypovolemia. *Ann Intern Med* 1986;104:298-303.
5. Frohlich ED, Tarazi RC, Dustan HP. Hyperdynamic beta-adrenergic circulatory state: increased beta-receptor responsiveness. *Arch Intern Med* 1969;123:1-7.
6. Shannon JR, Jordan J, Black BK, Diedrich A, Biaggioni I, Robertson D. Sympathetic support of the circulation in idiopathic orthostatic intolerance. *Circulation* 1998;98:Suppl I:I-336. abstract.
7. Narkiewicz K, Somers VK. Chronic orthostatic intolerance: part of a spectrum of dysfunction in orthostatic cardiovascular homeostasis? *Circulation* 1998;98:2105-7.
8. Jacob G, Shannon JR, Black B, et al. Effects of volume loading and pressor agents in idiopathic orthostatic tachycardia. *Circulation* 1997;96:575-80.
9. Jacob G, Shannon JR, Costa F, et al. Abnormal norepinephrine clearance and adrenergic receptor sensitivity in idiopathic orthostatic intolerance. *Circulation* 1999;99:1706-12.
10. Jordan J, Shannon JR, Black BK, Paranjape SY, Barwise J, Robertson D. Raised cerebrovascular resistance in idiopathic orthostatic intolerance: evidence for sympathetic vasoconstriction. *Hypertension* 1998;32:699-704.
11. Shannon JR, Flatter NL, Jordan J, et al. Orthostatic intolerance and tachycardia associated with norepinephrine-transporter deficiency. *N Engl J Med* 2000;342:541-9.
12. Boudoulas H, Reynolds JC, Mazzaferrri E, Wooley CF. Metabolic studies in mitral valve prolapse syndrome: a neuroendocrine-cardiovascular process. *Circulation* 1980;61:1200-5.
13. Frohlich ED, Dustan HP, Page IH. Hyperdynamic beta-adrenergic circulatory state. *Arch Intern Med* 1966;117:614-9.
14. Pasternac A, Tubau JF, Puddu PE, Krol RB, de Champlain J. Increased plasma catecholamine levels in patients with symptomatic mitral valve prolapse. *Am J Med* 1982;73:783-90.
15. 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;103:128-33.
16. 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;111:326-35.
17. Gruchalla R. Southwestern Internal Medicine Conference: masocytosis: developments during the past decade. *Am J Med Sci* 1995;309:328-38.
18. Streeten DH. Pathogenesis of hyperadrenergic orthostatic hypotension: evidence of disordered venous innervation exclusively in the lower limbs. *J Clin Invest* 1990;86:1582-8.
19. Hoeldtke RD, Dworkin GE, Gaspar SR, Israel BC. Sympathotonic orthostatic hypotension: a report of four cases. *Neurology* 1989;39:34-40.
20. Hoeldtke RD, Davis KM. The orthostatic tachycardia syndrome: evaluation of autonomic function and treatment with octreotide and ergot alkaloids. *J Clin Endocrinol Metab* 1991;73:132-9.
21. Low PA, Caskey PE, Tuck RR, Fealey RD, Dyck PJ. Quantitative sudomotor axon reflex test in normal and neuropathic subjects. *Ann Neurol* 1983;14:573-80.
22. Schonendorf R, Low PA. Idiopathic postural orthostatic tachycardia syndrome: an attenuated form of acute pandysautonomia? *Neurology* 1993;43:132-7.
23. Campbell TJ, Frohman B, Reeve EB. A simple, rapid, and accurate method of extracting T-1824 from plasma, adapted to the routine measurement of blood volume. *J Lab Clin Med* 1958;52:768-77.
24. 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;81:213-20.
25. Mosqueda-Garcia R. Evaluation of the autonomic nervous system: In: Robertson D, Biaggioni I, eds. Disorders of the autonomic nervous system. London: Harwood Academic, 1995:25-59.
26. Siggaard-Andersen J. Venous occlusion plethysmography on the calf: evaluation of diagnosis and results in vascular surgery. *Dan Med Bull* 1970;17:Suppl I:1-68.
27. Vissing SF, Scherrer U, Victor RG. Relation between sympathetic outflow and vascular resistance in the calf during perturbations in central venous pressure: evidence for cardiopulmonary afferent regulation of calf vascular resistance in humans. *Circ Res* 1989;65:1710-7.
28. Esler M, Jennings G, Lambert G, Meredith I, Horne M, Eisenhofer G. Overflow of catecholamine neurotransmitters to the circulation: source, fate, and functions. *Physiol Rev* 1990;70:963-85.
29. Scriven AJ, Brown MJ, Murphy MB, Dollery CT. Changes in blood pressure and plasma catecholamines caused by tyramine and cold exposure. *J Cardiovasc Pharmacol* 1984;6:954-60.
30. Rea RF, Eckberg DL, Fritsch JM, Goldstein DS. Relation of plasma norepinephrine and sympathetic traffic during hypotension in humans. *Am J Physiol* 1990;258:R982-R986.
31. Rapoport RM, Takimoto GS, Cho AK. Compartmental analysis of tyramine-induced norepinephrine depletion. *Pharmacology* 1981;23:235-42.
32. Schafers RF, Poller U, Ponick K, et al. Influence of adrenoceptor and muscarinic receptor blockade on the cardiovascular effects of exogenous noradrenaline and of endogenous noradrenaline released by infused tyramine. *Naunyn Schmiedeberg's Arch Pharmacol* 1997;355:239-49.
33. Scriven AJ, Dollery CT, Murphy MB, Macquinn I, Brown MJ. Blood pressure and plasma norepinephrine concentrations after endogenous norepinephrine release by tyramine. *Clin Pharmacol Ther* 1983;33:710-6.
34. Aneman A, Eisenhofer G, Olbe L, et al. Sympathetic discharge to mesenteric organs and the liver: evidence for substantial mesenteric organ norepinephrine spillover. *J Clin Invest* 1996;97:1640-6.
35. Grossman E, Chang PC, Hoffman A, Tamrat M, Kopin IJ, Goldstein DS. Tracer norepinephrine kinetics: dependence on regional blood flow and the site of infusion. *Am J Physiol* 1991;260:R946-R952.
36. Cousineau D, Rose CP, Goresky CA. Plasma expansion effect on cardiac capillary and adrenergic exchange in intact dogs. *J Appl Physiol* 1986;60:147-53.
37. Hague K, Lento P, Morgello S, Caro S, Kaufmann H. The distribution of Lewy bodies in pure autonomic failure: autopsy findings and review of the literature. *Acta Neuropathol (Berl)* 1997;94:192-6.
38. Kanda T, Tomimitsu H, Yokota T, Ohkoshi N, Hayashi M, Mizusawa H. Unmyelinated nerve fibers in sural nerve in pure autonomic failure. *Ann Neurol* 1998;43:267-71.
39. Hickler RB, Thompson GR, Fox LM, Hamlin JT III. Successful treatment of orthostatic hypotension with 9-alpha-fluorohydrocortisone. *N Engl J Med* 1959;261:788-91.
40. Bradbury S, Eggleston C. Postural hypotension: an autopsy upon a case. *Am Heart J* 1927;3:105-6.
41. Onrot J, Goldberg MR, Hollister AS, Biaggioni I, Robertson RM, Robertson D. Management of chronic orthostatic hypotension. *Am J Med* 1986;80:454-64.
42. Jordan J, Shannon JR, Biaggioni I, Norman R, Black BK, Robertson D. Contrasting actions of pressor agents in severe autonomic failure. *Am J Med* 1998;105:116-24.
43. Fouad-Tarazi FM, Okabe M, Goren H. Alpha sympathomimetic treatment of autonomic insufficiency with orthostatic hypotension. *Am J Med* 1995;99:604-10.
44. Convertino VA, Brock PJ, Keil LC, Bernauer EM, Greenleaf JE. Exercise training-induced hypovolemia: role of plasma albumin, renin, and vasopressin. *J Appl Physiol* 1980;48:665-9.