Abnormal Norepinephrine Clearance and Adrenergic Receptor Sensitivity in Idiopathic Orthostatic Intolerance

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Background—Chronic orthostatic intolerance (OI) is characterized by symptoms of inadequate cerebral perfusion with standing, in the absence of significant orthostatic hypotension. A heart rate increase of $\geq 30$ bpm is typical. Possible underlying pathophysologies include hypovolemia, partial dysautonomia, or a primary hyperadrenergic state. We tested the hypothesis that patients with OI have functional abnormalities in autonomic neurons regulating cardiovascular responses.

Methods and Results—Thirteen patients with chronic OI and 10 control subjects underwent a battery of autonomic tests. Systemic norepinephrine (NE) kinetics were determined with the patients supine and standing before and after tyramine administration. In addition, baroreflex sensitivity, hemodynamic responses to bolus injections of adrenergic agonists, and intrinsic heart rate were determined. Resting supine NE spillover and clearance were similar in both groups. With standing, patients had a greater decrease in NE clearance than control subjects ($55 \pm 6$% versus $30 \pm 7$%, $P=0.02$). After tyramine, NE spillover did not change significantly in patients but increased $50 \pm 10$% in control subjects ($P<0.001$). The dose of isoproterenol required to increase heart rate 25 bpm was lower in patients than in control subjects (0.5 $\pm 0.05$ versus $1.0 \pm 0.1$ $\mu g$, $P<0.005$), and the dose of phenylephrine required to increase systolic blood pressure 25 mm Hg was lower in patients than control subjects (105 $\pm 11$ versus $210 \pm 12$ $\mu g$, $P<0.001$). Baroreflex sensitivity was lower in patients ($12 \pm 1$ versus $18 \pm 2$ ms/mm Hg, $P<0.02$), but the intrinsic heart rate was similar in both groups.

Conclusions—The decreased NE clearance with standing, resistance to the NE-releasing effect of tyramine, and increased sensitivity to adrenergic agonists demonstrate dramatically disordered sympathetic cardiovascular regulation in patients with chronic OI. (Circulation. 1999;99:1706-1712.)

Key Words: norepinephrine receptors, adrenergic, alpha receptors, adrenergic, beta nervous system, autonomic

C hronic orthostatic intolerance (OI) (Table 1) is characterized by tachycardia and symptoms of cerebral hypoperfusion and sympathetic activation, which may include lightheadedness, anxiety, clouding of thought, visual changes, diaphoresis, nausea, and chest discomfort. The symptoms and tachycardia become manifest with assumption of upright posture and are relieved by sitting or lying down.

The pathophysiology of OI is poorly understood and probably heterogeneous. Features such as increased vascular resistance while supine$^1$ and a baseline hypovolemia$^1,2$ favor a primary hyperadrenergic state, whereas hypersensitivity of foot veins to local norepinephrine infusion$^3$, excessive pooling of blood in the lower extremities with standing$^4$, prolonged sympathetic nerve conduction velocities$^5$, and impaired responses to the quantitative sudomotor axon-reflex test$^6$ are consistent with lower-extremity sympathetic denervation.$^7$ We have shown improvement in symptoms with volume repletion and with acute administration of the $\alpha_1$-adrenergic receptor agonist midodrine and worsening of symptoms with acute administration of clonidine.$^8$ These findings suggest that the underlying pathophysiology of this disorder involves dysregulation of autonomic neurons or their associated adrenergic receptors.

To test this hypothesis, we determined norepinephrine spillover in patients with chronic OI and in normal control subjects in the supine and upright positions and after administration of pharmacological agents.
TABLE 1. Terms Used for Chronic Orthostatic Intolerance

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td>Idiopathic orthostatic intolerance</td>
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<tr>
<td>Idiopathic orthostatic tachycardia</td>
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<tr>
<td>Postural orthostatic tachycardia syndrome</td>
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<tr>
<td>Orthostatic tachycardia syndrome</td>
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<tr>
<td>Hyperadrenergic postural hypotension</td>
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<tr>
<td>Sympathotonic orthostatic hypotension</td>
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<tr>
<td>Hyperdymic β-adrenergic state</td>
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<tr>
<td>Idiopathic hypovolemia</td>
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<tr>
<td>Mitral valve prolapse syndrome</td>
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<td>Soldier’s heart</td>
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<td>Vasovagal asthenia</td>
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<td>Irritable heart</td>
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<td>Orthostatic anemia</td>
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<td>Chronic fatigue syndrome</td>
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Methods

Subjects

Thirteen patients (11 women, 2 men, 33±3 years old) referred to the Autonomic Dysfunction Center at Vanderbilt University between October 1994 and January 1996 for evaluation and treatment of symptoms consistent with chronic OI and 10 control subjects (8 women and 2 men, 34±2 years old) were studied. Patients were enrolled if they demonstrated an increase in heart rate of ≥30 bpm within 5 minutes of standing (without a decrease in blood pressure >20/10 mm Hg) on at least 3 occasions, had plasma norepinephrine ≥600 pg/mL with standing, and had at least a 6-month history of typical orthostatic symptoms (lightheadedness or dizziness, blurred vision, tremulousness, clamminess, palpitations, headache, chest discomfort, shortness of breath, nausea, anxiety, or presyncope) relieved with supine posture. Subjects with systemic illnesses capable of affecting autonomic function (eg, diabetes mellitus) were excluded. No subject had a history of alcohol, drug abuse, or a primary psychiatric disorder. Thyroid and adrenal dysfunction were ruled out by appropriate laboratory tests. Many patients had had extensive prior evaluation. All subjects had had echocardiograms and 24-hour Holter monitoring. Many had had cranial MRI scans. Several had undergone treadmill exercise testing, electrophysiologic testing, and even cardiac catheterization. All these studies were normal.

All investigational procedures were approved by the Vanderbilt Investigational Review Board, and subjects gave informed consent before the study. Medications were discontinued ≥2 weeks before the study, and no smoking was permitted. A questionnaire was administered to determine the type and extent of clinical symptoms, medical history, and associated diagnoses. Three days before admission, subjects began a diet containing 150 mEq Na+, 70 mEq K+, per day, no caffeine, and low monoamines, which was continued throughout the study. Subjects were admitted for study procedures to the Elliot V. Newman Clinical Research Center at Vanderbilt University, where sodium balance was confirmed with urinary Na+, K+, and creatinine monitoring.

Blood pressure, heart rate, and plasma catecholamines were determined in the supine and upright positions. Standard autonomic function tests were performed. Later, the effects of upright posture and of intravenous tyramine on norepinephrine kinetics were determined. On the following morning, responses to adrenergic receptor agonists were assessed.

Protocol

Autonomic Function Tests and Plasma Catecholamine Changes With Posture

Blood pressure, heart rate, and plasma catecholamines were determined after subjects had remained supine and had taken nothing by mouth overnight and again after 5 and 30 minutes of standing. Autonomic function tests were performed as previously described. The sinus arrhythmia ratio and the Valsalva ratio were used as indices of cardiac parasympathetic control. Cardiovascular sympathetic responses were assessed by evaluating the hypertensive response to hyperventilation and the hypertensive response to sustained handgrip and to immersion of the hand in ice water.

Effects of Posture and Tyramine on Norepinephrine Release

The study was conducted ≥2 hours after the last meal. Thirty minutes before the study, bilateral antecubital hepatic locks were placed for drug infusion and blood sampling. [3H]Norepinephrine was prepared immediately before use by diluting sterile pyrogen-free 1-[2,5,6-3H]norepinephrine (DuPont New England Nuclear) of high specific activity (50 to 60 Ci/mmol) in 0.9% saline. After a loading dose of 25 µCi was administered over 2 minutes, an infusion of 1 µCi/min was continued for 30 minutes. A baseline sample for norepinephrine and [3H]norepinephrine determination was then drawn from the contralateral arm. The patient then stood quietly for 30 minutes. Blood was obtained at 20 and 30 minutes for norepinephrine and [3H]norepinephrine determination. With the [3H]norepinephrine infusion continuing, the subject resumed the supine position. After 15 minutes, tyramine was administered intravenously. Heart rate was monitored with an ECG, and beat-to-beat blood pressure was monitored plethysmographically (Finapres, Ohmeda 2300). For analysis, brachial blood pressure was determined manually at baseline and every several minutes thereafter. The pulse pressure from the plethysmograph was adjusted for the average of ≥3 consecutive simultaneously determined brachial blood pressures to ensure its accuracy. Incremental bolus doses of tyramine (0.5, 1.0, 1.5, 2.0, and 3.0 mg) were administered to increase systolic blood pressure by 25 mm Hg. Blood was obtained from the contralateral arm vein for norepinephrine and [3H]norepinephrine determination at the maximal pressor effect after the final tyramine dose.

Three milliliters of [3H]norepinephrine infusate were collected and frozen at the end of each study to determine the specific activity. The concentrations of [3H]norepinephrine in plasma and the infusate were measured in fractions of the column effluent corresponding to the retention time of norepinephrine. Fractions were collected in scintillation vials, and the specific activity was assayed by liquid scintillation counting (LS 6000IC, Beckman Instruments Inc). Radioactivity (dpm/min) was adjusted for background, for the volume of extracted plasma injected into the high-performance liquid chromatograph (75 to 100 µL), and for recovery through the alumina extraction step.

Whole-body plasma norepinephrine clearance (systemic clearance) was determined as follows: Systemic clearance=[3H]norepinephrine infusion rate (dpm/min)/plasma [3H]norepinephrine (dpm/L).

Plasma norepinephrine appearance rate (systemic spillover) was determined as follows: Systemic spillover (µg/min)=systemic clearance (L/min)×plasma norepinephrine concentration (µg/L).

Pharmacological Tests

Subjects were studied lying supine in a quiet, partially darkened room ≥2 hours after their last meal. Blood pressure and heart rate were determined as described for the tyramine test. Incremental bolus doses of drugs were administered to achieve the end points described below. Boluses were administered in <1 second via an antecubital hepatic lock placed ≥1 hour before study. Four or 5 boluses of each drug were administered with 5 to 10 minutes allowed to elapse between each bolus for return to baseline.

Responses to Adrenergic Agonists

Isoproterenol (starting at 0.125 µg) was administered in incremental bolus doses until heart rate increased by 25 bpm or systolic blood pressure decreased by 25 mm Hg. Phenylephrine (starting at 12.5 µg) was administered to increase systolic blood pressure by 25 mm Hg. Nitroprusside (starting at 0.1 µg/kg) was administered to decrease systolic blood pressure by 25 mm Hg. Tyramine (starting at...
Results
Orthostatic lightheadedness/dizziness, visual changes, palpitations, chest discomfort, shortness of breath, nausea, fatigue, and exercise intolerance were the most common complaints (Table 2). Although 39% of patients had had syncope (usually after prolonged standing), they had learned to avoid syncope by sitting or lying down as symptoms built in intensity. Fatigue was common (10 of 13 subjects), but only 3 subjects met the criteria for the chronic fatigue syndrome. In contrast to the intractable fatigue characteristic of the chronic fatigue syndrome, most subjects reported complete or partial relief by lying down. Twenty-three percent had symptoms consistent with irritable bowel syndrome. Although 46% carried the diagnosis of mitral valve prolapse, none had significant mitral regurgitation or evidence of myxomatous degeneration.

Heart rate in patients increased 54±3 bpm after 30 minutes of standing (Table 3) compared with 14±2 bpm in control subjects. The change in systolic blood pressure with standing was similar in patients and control subjects, but patients had a greater increase in diastolic blood pressure with standing. Supine and upright norepinephrine and epinephrine levels were greater in patients than in control subjects. In control subjects, plasma norepinephrine and epinephrine increased at 5 minutes of standing but did not significantly increase further after 30 minutes of standing. In contrast, plasma norepinephrine and epinephrine continued to increase in patients during the 30 minutes of standing.

Autonomic Function Tests
Parasympathetic cardiovascular control was similar in patients and control subjects (Table 4). After sympathetic and parasympathetic blockade, heart rates were similar in patients and control subjects (Figure 1). Compared with control subjects, patients had a significantly greater heart rate increase with hyperventilation and a greater systolic blood pressure increase with sustained handgrip.

Norepinephrine Spillover: Supine and Standing
Supine norepinephrine spillover was similar in patients and control subjects (1.9±0.3 versus 1.8±0.3 µg/min, respectively), as was supine norepinephrine clearance (6.9±0.4 versus 6.8±0.9 L/min, respectively). The increase in norepinephrine spillover after 30 minutes of standing was similar in patients (60±12%) and control subjects (80±30%). This increase in norepinephrine spillover was associated with a decrease in norepinephrine clearance in both groups, but the decreased
The effects of tyramine on plasma norepinephrine and on norepinephrine spillover are depicted in Figure 3. Tyramine increased plasma norepinephrine in a dose-dependent fashion in both groups. In control subjects, tyramine (3 mg) increased norepinephrine spillover by 50 ± 10% and clearance by 10 ± 10%. In patients, tyramine failed to increase norepinephrine spillover and decreased clearance by 18 ± 8%.

### Table 3: Supine and Upright (5 and 30 Minutes) Heart Rate, Blood Pressure, and Plasma Catecholamines of Patients and Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Control Subjects</th>
<th>P, Patients vs Control Subjects</th>
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<tbody>
<tr>
<td></td>
<td>Supine</td>
<td>Upright, 5 min</td>
<td>Upright, 30 min</td>
</tr>
<tr>
<td></td>
<td>Supine</td>
<td>Upright, 5 min</td>
<td>Upright, 30 min</td>
</tr>
<tr>
<td>Start time</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>HR, bpm</td>
<td>70±2</td>
<td>120±3</td>
<td>130±3</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>114±3</td>
<td>111±4</td>
<td>109±4</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>69±2</td>
<td>74±3</td>
<td>77±3</td>
</tr>
<tr>
<td>NE, pg/mL</td>
<td>288±45</td>
<td>845±70</td>
<td>1270±90</td>
</tr>
<tr>
<td>EPI, pg/mL</td>
<td>39±5</td>
<td>75±7</td>
<td>90±15</td>
</tr>
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</table>

HR indicates heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; NE, norepinephrine; and EPI, epinephrine.

### Table 4: Autonomic Function Tests and Intrinsic Heart Rate

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects</th>
<th>Patients</th>
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<tr>
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<tr>
<td>Vagal function indexes</td>
<td></td>
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<tr>
<td>Valsalva ratio</td>
<td>1.86±0.08</td>
<td>1.95±0.05</td>
</tr>
<tr>
<td>Sinus arrhythmia ratio</td>
<td>1.37±0.04</td>
<td>1.48±0.05</td>
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</table>

Sympathetic function indexes

- Hyperventilation ∆HR, bpm
- Hyperventilation ∆BP, mm Hg
- Handgrip ∆BP, mm Hg
- Cold pressor test ∆BP, mm Hg

Intrinsic heart rate

- Observed
- Predicted

ΔHR indicates heart rate changes; ∆BP, blood pressure changes (systolic/diastolic).

*P<0.04, †P<0.01.

### Intrinsic Heart Rate

The intrinsic heart rate (Table 4) was similar in both groups and was not different from the predicted values (118.1–(0.57×age)). Propranolol decreased the heart rate more in patients than in control subjects (17±1 versus 10±1 bpm, P<0.001), but subsequent administration of atropine increased heart rate similarly in both groups (42±3 bpm in patients versus 40±3 bpm in control subjects) (Figure 1).

### Discussion

Several new observations regarding the physiological and biochemical characteristics of patients with chronic OI emerge from this study. First, although most of the increase in plasma norepinephrine in normal subjects occurs in the first 5 minutes of standing, plasma norepinephrine continues to increase in patients for at least 30 minutes. Second, although norepinephrine spillover and clearance are similar in patients and normal subjects when supine, spillover fails to increase and clearance actually decreases with upright posture in patients. Third, tyramine causes a smaller increase in norepinephrine spillover in patients than in control subjects. Fourth, patients are more sensitive to the heart rate–increasing effect of isoproterenol and the blood pressure–increasing effect of phenylephrine, patients required more tyramine than control subjects to increase systolic blood pressure 25 mm Hg (TYR25) (3.0±0.2 versus 2.1±0.1 mg, P<0.01). The dose of the nitric oxide donor nitroprusside necessary to decrease systolic blood pressure 25 mm Hg (NTP25) was similar in patients and control subjects (1.2±0.05 versus 1.4±0.1 μg/kg).

**Figure 1.** Change in heart rate (∆HR, bpm) after propranolol (0.2 mg/kg in 4 doses) followed by atropine (0.04 mg/kg in 4 doses).
phenylephrine than normal subjects, and they are less sensitive to the blood pressure–increasing effect of tyramine.

Chronic OI is characterized by orthostatic symptoms of cerebral hypoperfusion with orthostatic tachycardia and without significant orthostatic hypotension. As evidenced by the many incarnations emerging throughout the years (Table 1), multiple disorders probably exist that present with similar hemodynamic and symptomatic manifestations. Perhaps it is this diversity that has made understanding the pathophysiology of OI so difficult. We attempted to minimize the problem of subject diversity by using stringent criteria to secure as homogeneous a study population as possible. All subjects consistently had a 30-bpm orthostatic heart rate increase, but they did not have orthostatic hypotension. Special care was taken to ensure that symptoms themselves were truly exacerbated by upright posture and were minimal or not present while patients were supine or seated. To exclude individuals who might have an acute or transient hemodynamic problem, we studied only patients who had had symptoms for >6 months. A standing norepinephrine of 600 pg/mL ensured that patients with relatively mild symptoms would be excluded.

The primary aim of the study was to define the norepinephrine kinetics and dynamics and adrenergic receptor sensitivity in patients with relatively severe OI. As expected from the selection criteria, upright norepinephrine was greater in patients than in control subjects. Supine norepinephrine was also greater in patients. Although the increase in norepinephrine spillover with standing was similar in patients and control subjects, the decrease in clearance was greater in patients than control subjects, indicating that much of the increase in plasma norepinephrine was due to a decrease in clearance. A decrease in norepinephrine clearance could be due to a decrease in cardiac output resulting from pooling of blood in the lower extremities, hypovolemia, a reduction in liver blood flow, or a combination of these mechanisms. Maneuvers to prevent pooling and maintain cardiac output, such as volume expansion and the use of an inflatable pressure suit, improve hemodynamics in similar patients.

Decreased cardiac output with standing, however, may not completely explain the hemodynamic and biochemical abnormalities observed in these patients. The results of the tyramine test give additional information. Tyramine has little direct effect on α- and β-adrenergic receptors, but it causes release of norepinephrine from neuronal stores, which then becomes available to act on these receptors. Thus, tyramine allows assessment of intraneuronal stores of norepinephrine. Tyramine increased norepinephrine spillover less in patients with OI than in control subjects, suggesting that either their neuronal stores of norepinephrine are decreased or the release is somehow impaired. Decreased norepinephrine stores could result from a decrease in the numbers of noradrenergic neurons or from impaired synthesis or storage of norepinephrine in otherwise intact neurons. Impairment in

**Figure 2.** Change in systemic norepinephrine spillover (a) and clearance (b) from supine after 20 and 30 minutes of standing in 13 patients with chronic OI (○) and 10 control subjects (●).

**Figure 3.** Effect of tyramine boluses of 2 mg (hatched bars) and 3 mg (solid bars) on changes in plasma norepinephrine (a), systemic norepinephrine spillover (b), and systemic norepinephrine clearance (c).
the norepinephrine transporter reducing entry of tyramine into the neuron could also cause the decreased norepinephrine spillover observed in patients.

The observation of tyramine resistance and hypersensitivity to the pressor effect of phenylephrine, although less marked, is reminiscent of observations in patients with pure autonomic failure, in which loss of postganglionic autonomic neurons is thought to underlie the pathophysiology. These findings could also be explained by alterations in the capacity of the baroreflex to buffer changes in blood pressure. Although our patients had decreased baroreflex sensitivity, the degree of hyposensitivity in individual patients did not correlate with their baroreflex slope.

Patients were hypersensitive to the heart rate–increasing effect of bolus injections of isoproterenol. In addition to its direct effect on heart rate due to stimulation of β1-adrenergic receptors, isoproterenol also stimulates β2-adrenergic receptors, causing vasodilation. The resulting decrease in blood pressure indirectly contributes to tachycardia through baroreflex activation. To control for this phenomenon, we corrected the heart rate responses to isoproterenol to individual baroreflex sensitivity and still noted an apparent β2-adrenergic receptor hypersensitivity. Apparent β2-adrenergic receptor hypersensitivity has been demonstrated previously in similar patient populations. However, none of these studies (including ours) tested direct β2-adrenergic receptor sensitivity by local infusion into the coronary arteries.

Apparent β2- and α1-adrenergic receptor hypersensitivity in the setting of high circulating catecholamines is paradoxical. This paradox may be resolvable when the location of these receptors is considered. Although both β2- and α1-adrenergic receptors are innervated receptors (ie, they are modulated primarily by the local release of neuronal norepinephrine into the synaptic cleft), β2-adrenergic receptors are often “humoral” receptors that are influenced primarily by circulating catecholamines. Reduced local norepinephrine release onto β2- and α1-adrenergic receptors could lead to their upregulation, whereas high circulating norepinephrine and epinephrine could prevent the development of hypersensitivity of β2-adrenergic receptors. The exaggerated response to agonists of the 2 innervated receptors, the lack of hypersensitivity of the humoral receptor, and resistance to the norepinephrine-releasing effect of tyramine are consistent with a functional abnormality of sympathetic nerves or distorted architecture of the synapse.

The orthostatic tachycardia seen in these patients could be due to a combination of β2-adrenergic receptor hypersensitivity and high circulating catecholamines. Vagal impairment or increased central sympathetic drive could also contribute. Although demonstration of normal vagal cardiovascular regulation and intrinsic heart rate in the present study argues against a parasympathetic defect, our results differ from those of Morillo et al, who observed an increased intrinsic heart rate in somewhat similar patients. Perhaps determining intrinsic heart rate by some other method may help clarify its contribution to OI. Although there is microneurographic evidence of increased sympathetic traffic in similar patients while they are supine, sympathetic traffic in the upright posture is not excessive.

The elevated plasma epinephrine in our patients warrants comment. Epinephrine is a potent α1- and β2-adrenergic receptor agonist. Stimulation of presynaptic β2-adrenergic receptors could augment norepinephrine release. In addition, uptake by the norepinephrine transporter of circulating epinephrine into noradrenergic neurons and its subsequent release could alter the response to systemic sympathetic activation, perhaps resulting in activation that is more pronounced or having more of a β2-adrenergic character, as has been proposed in the epinephrine theory of hypertension.

In summary, patients with chronic OI have multiple abnormalities of cardiovascular autonomic regulation, including elevated circulating plasma norepinephrine and epinephrine associated with significantly impaired norepinephrine clearance, apparent hypersensitivity of innervated (α1- and β2-) but not humoral (β2-) adrenergic receptors, and a decrease in the capacity of tyramine to increase norepinephrine spillover consistent with reduction in neuronal norepinephrine stores. Taken together, these findings are consistent with a partial sympathetic dysautonomia in these patients. Whether this partial dysautonomia is functional or anatomic is not clear,
nor is it clear whether the primary abnormality is one of peripheral autonomic function or central regulatory mechanisms. Many (but not all) findings reported in these patients are consistent with dysregulation of noradrenergic neurons in certain distributions. Such a dysregulation might arise from a process that evoked excitotoxicity or other toxicity to noradrenergic neurons or their connections. Finally, the role of norepinephrine transporter function in the dramatic abnormalities in catecholamine clearance must receive increased attention in future studies.

Acknowledgments
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