Increased Sympathetic Activation in Idiopathic Orthostatic Intolerance
Role of Systemic Adrenoreceptor Sensitivity

Jens Jordan, John R. Shannon, Andre Diedrich, Bonnie K. Black, David Robertson

Abstract—Idiopathic orthostatic intolerance (OI) is characterized by adrenergic symptoms with standing. Changes in central sympathetic tone or in adrenoreceptor sensitivity could contribute to this syndrome. In OI patients and control subjects, we determined heart rate (HR) and systolic blood pressure (SBP) changes after incremental bolus doses of isoproterenol and phenylephrine before and during ganglionic blockade with trimethaphan. SBP decreased by $17 \pm 1.6$ mm Hg in patients and $3.9 \pm 3.8$ mm Hg in control subjects ($P<0.01$) with trimethaphan. Patients with a larger decrease ($28 \pm 3.8$ mm Hg, $n=7$) in SBP with trimethaphan had greater supine SBP and supine and upright plasma norepinephrine levels than did patients with a lesser decrease ($3.0 \pm 3.0$ mm Hg, $n=7$) in SBP. Supine and orthostatic HRs were similar for the groups. The majority of patients had a normal HR response to isoproterenol before and during ganglionic blockade. Phenylephrine increased SBP similarly in patients and control subjects before and during blockade. Sympathetic support is increased in a subgroup of OI patients. Hyperadrenergic and nonhyperadrenergic subgroups have similar degrees of orthostatic tachycardia. Our findings suggest that the hyperadrenergic features of OI cannot be completely explained by systemic hypersensitivity of postsynaptic $\alpha_1$- and $\beta$-adrenoreceptors but rather originates in enhanced sympathetic activation. (Hypertension. 2002;39:173-178.)

Key Words: autonomic nervous system ■ tachycardia ■ postural tachycardia syndrome ■ receptors, adrenergic

Idiopathic orthostatic intolerance (OI) is a common syndrome of unknown cause characterized by orthostatic adrenergic symptoms in the absence of orthostatic hypotension but accompanied by $\geq 30$-bpm orthostatic increase in heart rate.1–4 Increased muscle sympathetic nerve activity while supine5 and elevated heart rate and plasma norepinephrine concentrations in the supine position and with standing6,7 suggest that sympathetic outflow is increased in both the supine and upright positions. However, systemic norepinephrine spillover in OI patients is similar to that of normal control subjects in both the supine and standing positions,7 and muscle sympathetic nerve activity with upright posture in OI patients is not excessive compared with that of control subjects.5 Thus, the hyperadrenergic features of OI might not simply be due to increased central sympathetic outflow and norepinephrine release: rather norepinephrine, once released, could have an augmented effect in OI patients. Indeed, some OI patients are hypersensitive to the tachycardic effect of isoproterenol, a nonselective $\beta$-adrenoceptor agonist,7,8 and have a greater pressor response to phenylephrine, an $\alpha_1$-adrenergic agonist.7 However, estimation of systemic adrenoceptor sensitivity based on systemic administration of agonists is confounded by baroreflex-mediated changes in autonomic nervous system activity.9 Ganglionic blockade is a useful technique to discern the contribution of sympathetic and parasympathetic activity to overall support of the circulation and to study the sensitivity of adrenoreceptors in the absence of baroreflex buffering.9,10 We used this technique to test the hypothesis that the contribution of sympathetic tone to resting heart rate and blood pressure is indeed increased in patients with OI. Furthermore, we investigated whether increased systemic $\alpha_1$- and $\beta$-adrenoreceptor sensitivity contributes to the OI phenotype.

Methods

Subjects
We studied 14 patients with OI (13 women and 1 man, 19 to 50 years) who were subsequently hospitalized. We did not find significant hypersensitivity to isoproterenol or phenylephrine in the absence of ganglionic blockade in this group of patients. We confirmed this finding in additional patients (total: 21 women and 1 man, 19 to 50 years). We compared patients with 9 control subjects (7 women and 2 man, 24 to 37 years) who were recruited from a pool of normal volunteers. All studies were approved by the Vanderbilt Investigational Review Board, and subjects gave informed consent before the study.
Protocol
Three days before the study, patients and control subjects were placed on a 150 mEq sodium and 70 mEq potassium diet free of substances that could interfere with catecholamine determinations. Medications were discontinued ≥5 half-lives before testing. Patients and control subjects underwent an autonomic evaluation that included the determination of orthostatic vital signs, controlled breathing, a Valsalva maneuver, hyperventilation, handgrip testing, cold pressor testing, and pharmacological testing. Venous blood samples for measurement of plasma catecholamine concentrations, plasma renin activity, and plasma aldosterone concentrations were obtained after an overnight rest in the supine position and again after 30 minutes in the standing position.

Pharmacological Testing
Pharmacological testing was performed with subjects in the supine position as described previously. Heart rate was determined with continuous ECG, and blood pressure changes were measured on a beat-to-beat basis with photoplethysmography that was adjusted to brachial blood pressure measurements. Incremental bolus doses of isoproterenol, nitroprusside, and phenylephrine were administered into a large antecubital vein. Sympathetic and parasympathetic ganglia were then blocked using trimethaphan (Trimetaphan, Cambridge Labs). Bolus doses of phenylephrine (25 μg) and nitroprusside (0.4 μg/kg) were administered to assess the completeness of blockade. Bolus doses of test medications were then administered again. Blood was obtained for determination of plasma catecholamine concentration immediately before trimethaphan infusion and again after ganglionic blockade was achieved. Systolic blood pressure changes induced by phenylephrine or nitroprusside were plotted against corresponding changes in the R-R interval to determine baroreflex sensitivity.

Statistical Analysis
All data are expressed as mean±SEM. Intraindividual and interindiv-idual differences were analyzed by 2-tailed paired and unpaired t tests, respectively. If appropriate, 2-way ANOVA testing for repeated measures was used. A value of P<0.05 was considered to be statistically significant.

Results
Autonomic Evaluation
Supine blood pressure was similar in patients and control subjects (110±3.6/66±2.6 and 111±3.5/65±2.4 mm Hg, respectively). Systolic blood pressure did not change in patients with standing, but it decreased slightly in control subjects (−7±2 mm Hg, P<0.05). In both groups, diastolic blood pressure increased similarly with standing (8.2±2.6 mm Hg in patients, 6.4±2.2 mm Hg in control subjects). Supine heart rate was elevated in patients relative to control subjects (70±3 bpm, 69±4 bpm, P<0.05). With standing, the heart rate increased by 48±3.9 bpm in patients and 28±2.7 bpm in control subjects (P<0.01 between groups). Absence of orthostatic hypotension, normal respiratory sinus arrhythmia and Valsalva heart rate ratio, the absence of a depressor response to hyperventilation, and a normal cold pressor response in both groups are consistent with at least partially intact sympathetic and parasympathetic function.

In the supine position, the plasma norepinephrine concentration was 1.4±0.14 nmol/L (240±23 pg/mL) in patients and 0.79±0.083 nmol/L (130±14 pg/mL) in control subjects (P<0.05). After 30 minutes of standing, plasma norepinephrine concentration increased to 4.7±0.49 nmol/L (790±83 pg/mL) in patients and to 2.3±0.25 nmol/L (380±43 pg/mL) in control subjects. The ratio of dihydroxyphenylglycol (DHPG) to norepinephrine in the supine position was almost 2-fold smaller in patients than in control subjects (4.7±0.51 in patients, 8.8±0.91 in control subjects, P<0.001) (Figure 1). Supine and upright renin activities and supine aldosterone concentrations were similar in patients and control subjects. Upright aldosterone concentration tended to be higher in control subjects (28±4.6 versus 17±2.6 ng/dL, P=0.058). The change in aldosterone concentration with standing was significantly greater in control subjects than in patients (19±3.6 versus 6.4±2.2 ng/dL, P<0.05).

<table>
<thead>
<tr>
<th>Subgroups of OI Patients</th>
<th>Trimethaphan Response</th>
<th>Large Response</th>
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<tbody>
<tr>
<td>Orthostatic vital signs</td>
<td></td>
<td></td>
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<tr>
<td>Supine SBP, mm Hg</td>
<td>105±1.5†</td>
<td>127±8.0</td>
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<tr>
<td>SBP standing, mm Hg</td>
<td>0±4</td>
<td>1±3</td>
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<tr>
<td>Supine HR, bpm</td>
<td>70±3</td>
<td>69±4</td>
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<tr>
<td>HR standing, bpm</td>
<td>53±5</td>
<td>49±8</td>
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<td>Neurohumoral profile</td>
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<td>Supine norepinephrine, nmol/L</td>
<td>0.93±0.11†</td>
<td>1.85±0.24</td>
</tr>
<tr>
<td>Upright norepinephrine, nmol/L</td>
<td>3.4±0.49†</td>
<td>6.2±0.65</td>
</tr>
<tr>
<td>Supine epinephrine, nmol/L</td>
<td>0.34±0.16</td>
<td>0.15±0.03</td>
</tr>
<tr>
<td>Upright epinephrine, nmol/L</td>
<td>0.53±0.17‡</td>
<td>0.19±0.025</td>
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<tr>
<td>DHPG/norepinephrine supine</td>
<td>5.8±0.6†</td>
<td>3.2±0.3</td>
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<tr>
<td>Supine PRA, ng·L⁻¹·h⁻¹</td>
<td>1.5±0.17§</td>
<td>0.7±0.04</td>
</tr>
<tr>
<td>Upright PRA, ng·L⁻¹·h⁻¹</td>
<td>5.1±1.7</td>
<td>4.5±2.2</td>
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<tr>
<td>Supine aldosterone, ng/dL</td>
<td>11±2.3</td>
<td>11±2.3</td>
</tr>
<tr>
<td>Upright aldosterone, ng/dL</td>
<td>19±1.0</td>
<td>20±3.8</td>
</tr>
</tbody>
</table>

OI patients were stratified according to their depressor response to trimethaphan (smaller response, SBP decrease 6–1.5 mm Hg; larger response, SBP decrease 29±2.9 mm Hg). Results of pharmacological testing are given before trimethaphan infusion (isoproterenol 0.8 g, phenylephrine 200 g). SBP indicates systolic blood pressure; HR, heart rate; and PRA, plasma renin activity. *P<0.05, †P<0.01, ‡P=0.1, and §P=0.7.
Ganglionic Blockade

All control subjects tolerated the trimethaphan infusion. In contrast, the infusion had to be discontinued in 5 OI subjects because of symptomatic hypotension. In those patients tolerating the infusion, baroreflex slope decreased from 17±1.8 ms/mm Hg before trimethaphan to 0.5±0.2 ms/mm Hg during ganglionic blockade (Figure 2). In control subjects, the baroreflex slope decreased from 19±2 ms/mm Hg to 0.04±0.03 ms/mm Hg during ganglionic blockade. Patients had a greater decrease in systolic pressure with trimethaphan than did control subjects (−17±1.6 versus −3.9±3.8 mm Hg, P<0.01). Diastolic blood pressure changed by −7.0±2.7 mm Hg in OI patients and by −1±2.5 mm Hg in control subjects (P=NS between groups). Heart rate during ganglionic blockade was higher in OI patients (100±4.1 versus 88±2.5 bpm, P<0.01). With ganglionic blockade, plasma norepinephrine concentration decreased from 0.95±0.19 nmol/L (160±32 pg/mL) to 0.34±0.059 nmol/L (59±10 pg/mL) in control subjects and from 1.1±0.16 nmol/L (190±27 pg/mL) to 0.53±0.10 nmol/L (89±17 pg/mL) in patients.

Patients were stratified into 2 equal groups according to their depressor response to trimethaphan: those with a greater decrease (28±3.8 mm Hg) and those with a lesser decrease (3.0±3.0 mm Hg). Supine blood pressure was greater in the group with the greater depressor response to trimethaphan (Table). However, blood pressure during ganglionic blockade was similar between groups (96±8.9/72±4.7 mm Hg in greater responders, 101±1.2/64±3.3 mm Hg in lesser responders, P=NS). Supine heart rate and the increase in heart rate with standing were similar between groups. There were no significant differences between groups regarding responses to autonomic reflex testing and postural changes in renin and aldosterone. Patients with a large depressor response had both greater supine and upright plasma norepinephrine concentrations (Table). The supine DHPG/norepinephrine ratio tended to be lower in the group with the larger depressor response.

Sensitivity to Isoproterenol, Nitroprusside, and Phenylephrine

Before trimethaphan, the decrease in systolic blood pressure after a 0.8-μg bolus of isoproterenol was 12.6±2.9 mm Hg in control subjects and 8.15±2.66 mm Hg in patients (P=NS) (Figure 3). During trimethaphan, the same dose of isoproterenol decreased systolic blood pressure 34±3 and 32±1 mm Hg in control subjects and patients, respectively. With intact autonomic reflexes, isoproterenol at 0.8 μg increased the heart rate by 23±2 bpm in control subjects and 26±3 bpm in patients (P=NS). During ganglionic blockade, the same dose of isoproterenol increased the heart rate by 18±3 and 18±3 bpm in both control subjects and patients. In the larger group of patients, isoproterenol at 0.8 μg increased the heart rate by 29±2 bpm in the absence of ganglionic blockade (P=0.05 compared with control subjects). There was large overlap in the sensitivity to isoproterenol between patients and control subjects. There was no correlation between upright heart rate and isoproterenol sensitivity.

Before ganglionic blockade, 200 μg phenylephrine increased systolic blood pressure by 22±5.4 mm Hg in control subjects and 21±2.5 mm Hg in patients (P=NS) (Figure 4). During trimethaphan, a much smaller dose of phenylephrine (25 μg) increased systolic blood pressure by 23±2.7 and 21±1.4 mm Hg in control subjects and patients, respectively. In the larger group of patients, phenylephrine at 100 μg increased systolic blood by 16±1.6 mm Hg in the absence of trimethaphan (15±3.0 mm Hg in control subjects, P=0.4). Before ganglionic blockade, 0.4 μg/kg nitroprusside decreased systolic blood pressure by 8±2.7 mm Hg in control subjects and 9±1.3 mm Hg in patients (Figure 4). During trimethaphan, 0.2 μg/kg nitroprusside decreased systolic blood pressure by 13±1.6 mm Hg in control subjects and 13±1.0 mm Hg in patients.

Discussion

To study autonomic contribution to heart rate and blood pressure in OI patients, we used pharmacological ganglionic blockade. Trimethaphan at doses used in this study causes an almost complete loss of autonomic function.9-12 In a subgroup of OI patients, trimethaphan caused a greater decrease in blood pressure than in control subjects. Another subgroup of OI patients exhibited a similar sensitivity to trimethaphan as control subjects, yet both groups of patients had an almost identical increase in heart rate with standing.

The variability in the response to trimethaphan strongly suggests that the mechanisms underlying the syndrome OI differ from patient to patient. The group with a normal response to trimethaphan (“nonhyperadrenergic”) was remarkable in that they had no evidence of autonomic impairment in the supine position. This group may include patients with orthostatic intolerance secondary to excessive venous pooling in the lower extremities with standing.2 An increase in the depressor response to trimethaphan suggests that either the concentration of norepinephrine at adrenergic receptors is increased or that the released norepinephrine elicits a greater response. The group of “hyperadrenergic” patients exhibited an increase in plasma norepinephrine concentration in the supine and upright positions. The increase could be due to an increase in norepinephrine release or a decrease in norepinephrine clearance. In 1 study, systemic norepinephrine spillover was similar in OI patients and control subjects, whereas norepinephrine clearance was reduced.7 In contrast,
in another study, muscle sympathetic nerve activity in the supine position was increased in these patients.\textsuperscript{5} One explanation for these findings is that there is a mismatch between nerve traffic and norepinephrine release in some OI patients. For example, reduction in the number of sympathetic nerve fibers due to partial autonomic neuropathy\textsuperscript{2,13,14} could increase activity in the remaining neurons.

OI patients had smaller DHPG/norepinephrine ratios, which might be indicative of decreased neuronal uptake of norepinephrine.\textsuperscript{15} The group of patients with the larger response to trimethaphan had an even smaller DHPG/norepinephrine ratio. Decreased sensitivity to the norepinephrine-releasing effect of tyramine is further evidence for impaired norepinephrine uptake mechanisms in some OI patients.\textsuperscript{7} The impairment could be caused by an autonomic neuropathy\textsuperscript{2,13} or a functional defect of postganglionic sympathetic neurons. In the family of 1 of the OI patients who also participated in the present study, a functionally relevant base-pair change of the norepinephrine transporter gene was found that segregated with abnormalities in heart rate regulation and norepinephrine turnover.\textsuperscript{16,17} This patient and her identical twin sister had an excessive depressor response to trimethaphan.

In previous studies, some OI patients were hypersensitive to the tachycardic effect of isoproterenol, which was administered as a continuous intravenous infusion\textsuperscript{8} or an intravenous bolus.\textsuperscript{7} Similarly, OI patients were hypersensitive to the pressor effect of phenylephrine.\textsuperscript{7} In another study, however, the pressor sensitivity of OI patients to norepinephrine was within the normal range.\textsuperscript{2} In our study in a relatively large group of OI patients, the responses to phenylephrine and to isoproterenol in the absence of trimethaphan varied in patients and in control subjects. On average, patients tended to have a greater chronotropic response to isoproterenol than did control subjects, but there was a large overlap between groups. The phenylephrine response was similar in the 2 groups. Thus, increased sensitivity to the effect of adrenoceptor agonists may be a contributing factor to the pathogenesis of OI in a subgroup of patients. Sensitivities to phenylephrine and to isoproterenol were similar in “hyperadrenergic” and “nonhyperadrenergic” patients. Both groups had a similar increase in heart rate with standing and similar sensitivity to isoproterenol but different venous plasma norepinephrine levels. One possible explanation for the phenomenon is that the hyperadrenergic group has a more generalized sympathetic activation that is less targeted to the heart.

Because it is possible that a difference in adrenergic sensitivity to isoproterenol is masked by the baroreflex, we repeated testing with phenylephrine, isoproterenol, and nitroprusside during complete ganglionic blockade.\textsuperscript{9,18} OI patients
and control subjects had similar sensitivities to the pressor effect of phenylephrine or the tachycardic effect of isoproterenol during trimethaphan infusion. Moreover, the \(\beta\)-adrenoceptor–mediated depressor response to isoproterenol and the depressor response to nitroprusside were almost identical in both groups before and during trimethaphan infusion. These findings suggest that increased systemic sensitivity to postsynaptic \(\alpha_1\)- or \(\beta\)-adrenoceptors is not the crucial mechanism explaining the hyperadrenergic features of OI. Because we studied a relatively small number of patients, we cannot exclude that in some patients with OI, adrenoreceptor sensitivity is increased. We cannot exclude completely that the inability to study phenylephrine and isoproterenol responses during ganglionic blockade in the group who did not tolerate trimethaphan may have led to a systemic underestimation of adrenoreceptor sensitivity. The absence of systemic adrenoreceptor hypersensitivity does not exclude the possibility that local vascular beds, such as the foot veins, may exhibit hypersensitivity to adrenergic agonists.

We conclude that a subgroup of patients with OI exhibits a substantial increase in sympathetic support of the circulation even in the supine position. This hyperadrenergic group of OI patients is characterized by an increased plasma norepinephrine concentration in the supine and upright position and a decreased DHPG/norepinephrine ratio, which is suggestive of decreased neuronal uptake of norepinephrine. Another subgroup of OI patients has a similar degree of orthostatic tachycardia but no evidence of increased sympathetic support of the circulation. The chronotropic response to isoproterenol tended to be greater in OI patients than in control subjects. However, there is large overlap between patients and control subjects, and isoproterenol sensitivity is not related to the severity of orthostatic tachycardia. There was no evidence for a substantial increase in the sensitivity to adrenoreceptor stimulation during complete ganglionic blockade with trimethaphan. Thus, the hyperadrenergic features of OI cannot be completely explained by systemic hypersensitivity of postsynaptic \(\alpha_1\)- and \(\beta\)-adrenoceptors. Ganglionic blockade is a useful tool to characterize subgroups of patients in the setting of therapeutic and pathophysiological studies.

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References

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