Abnormal Baroreflex Responses in Patients With Idiopathic Orthostatic Intolerance

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Background—Patients diagnosed with idiopathic orthostatic intolerance report symptoms of lightheadedness, fatigue, and nausea accompanied by an exaggerated tachycardia when assuming the upright posture. Often, these symptoms are present in the absence of any decrease in arterial pressure. We hypothesized that patients with idiopathic orthostatic intolerance would have impaired cardiac vagal and integrated baroreflex function, lower blood volume, and increased venous compliance.

Methods and Results—Sixteen patients and 14 healthy control subjects underwent the modified Oxford technique to assess cardiac vagal baroreflex sensitivity. Progressive lower-body negative pressure (to –50 mm Hg; LBNP) was used to examine the integrated baroreflex response to progressive hypovolemic stimuli. Blood volume and venous compliance were also assessed. Patients with idiopathic orthostatic intolerance had lower cardiac vagal baroreflex sensitivity (12 ± 6 vs. 25 ± 4 ms/mm Hg; P < 0.01). The integrated baroreflex response to low levels of LBNP was characterized by shorter R-R intervals and more symptoms such as lightheadedness, despite similar levels of blood pressure. There was a trend toward lower blood volume in the patient group (56 ± 6 vs. 63 ± 3 mL/kg; P = 0.054).

Conclusions—Patients with idiopathic orthostatic intolerance have lower cardiac vagal baroreflex sensitivity and marginally lower blood volume and respond with faster heart rates despite similar levels of arterial pressure during LBNP. These findings may contribute to the exaggerated postural tachycardia and symptoms observed in patients with this disorder. (Circulation. 2000;102:3086-3091.)

Key Words: baroreceptors ▪ blood pressure ▪ tachycardia ▪ nervous system, autonomic

Estimates indicate that up to 500 000 Americans suffer from some form of orthostatic intolerance. A disproportionate number of women are affected.1 Diagnostic terms used to describe this idiopathic syndrome include postural orthostatic tachycardia syndrome, hyperadrenergic orthostatic tachycardia, idiopathic hypovolemia, partial dysautonomia, and chronic orthostatic intolerance.2–8 The pathophysiological basis of this disorder is unknown. However, all forms of idiopathic orthostatic intolerance encompass some combination of symptoms of lightheadedness, fatigue, nausea, palpitations, and cognitive impairment. Moreover, hemodynamically, an exaggerated tachycardia is apparent when upright posture is assumed, yet this feature typically occurs without any decrease in arterial pressure.

Despite the apparent maintenance of arterial pressure, deficits in cardiovascular regulation may play a primary role in this disorder. Cardiovascular adjustments to acute increases and decreases in arterial pressure require effective reflex responses to ensure appropriate autonomic outflow. Abnormalities in reflex autonomic control, blood volume, and blood volume distribution, alone or in combination, may result in orthostatic intolerance. However, to date, arterial and cardiopulmonary reflex gains and their relation to blood volume and its distribution have not been characterized in patients with idiopathic orthostatic intolerance.9

We hypothesized that impaired baroreflex function might be responsible for the features of this disorder. Baroreflex impairment has been associated with a hyperadrenergic state,10,11 thereby providing a possible explanation for the exaggerated tachycardia observed in this patient population. Furthermore, the inappropriate increase in heart rate and increased sympathetic outflow may cause some of the symptoms reported by this patient group.9 Reports of impaired vagal baroreflex function with an exaggerated tachycardia and orthostatic intolerance in young healthy men after head-down bed rest lend support to this hypothesis.12 We therefore assessed the cardiovagal baroreflex with the modified Oxford technique and the integrated baroreflex with lower-body negative pressure (LBNP) using low- and high-level hypovolemic stimuli.

Furthermore, because chronic hypovolemia and/or increased venous pooling may be contributing factors to symp-
toms of orthostatic intolerance, we also measured blood volume and lower-limb venous compliance. We hypothesized that patients with idiopathic orthostatic intolerance would have lower blood volume and increased venous compliance.

### Methods

**Subjects**

Sixteen patients and 14 healthy control subjects agreed to participate in this institutionally approved study. Patients recruited for the study had idiopathic orthostatic intolerance defined by symptoms of orthostatic intolerance and an increase in heart rate of >30 bpm within 10 minutes of standing without orthostatic hypotension.

Patients and control subjects were required to be free from any acute illness or chronic disease. All participants completed questionnaires, including the autonomic symptom questionnaire, orthostatic tolerance questionnaire, and fatigue severity scale.13

**Protocol Overview**

In the week preceding the protocol, subjects discontinued all medications for at least 5 half-lives and were instructed to follow a diet containing approximately 100 mg of sodium, 75 mg of potassium, 2500 mL of fluid, and >1800 kcal per day. Subjects were also asked to refrain from caffeine and alcohol consumption. Compliance to the assigned diet was assessed by use of a 5-day diet record. We controlled activity level, food intake, and fluid intake during the 2-day protocol by having subjects report to the clinical research center for the study duration.

**Day 1**

**Plasma and Blood Volume Determination**

Plasma volume was determined by a single bolus injection (3.0 to 3.5 mL) of Evans blue dye (New World Trading). Absorbance of the plasma samples was read with a spectrophotometer ( Beckman Spectrophotometer, Beckman Instruments Inc) at 620 nm 10, 20, and 30 minutes after the injection. Hematocrit (Hct) was determined with a microcentrifuge and corrected for peripheral sampling (0.91) and trapped plasma (0.96). Blood volume (BV) was calculated with the formula $BV = PV/(1 – Hct_{corr})$, where PV indicates plasma volume.14

**Venous Compliance**

Compliance of the left calf was assessed by a technique as outlined by Convertino et al.15 After 30 minutes of supine rest, a mercury-in-silastic strain gauge (D.E. Hokanson) was placed around the calf and an occlusion cuff around the thigh. The thigh cuff was inflated twice at 30 and 50 mm Hg for a period of 4 minutes. Percent volume change at the plateau point during the thigh cuff inflation was divided by the cuff pressure and used as an index of lower-leg venous compliance.

**Standard Autonomic Testing**

Baseline cardiac vagal function was determined by the difference between maximum and minimum heart rate during paced breathing. Supine subjects were trained to breathe deeply for 90 seconds at a rate of 6 breaths per minute. A Valsalva maneuver was performed in triplicate by having subjects expire for 15 seconds against a resistance of 40 mm Hg.16 These (and subsequent) data were recorded and digitized with WinDaq Data Acquisition Software (DATAQ Instruments).

**Day 2**

**Cardiac Vagal Baroreflex Sensitivity**

The modified Oxford technique17 was used to assess cardiac vagal baroreflex sensitivity. A bolus injection of the vasodilator sodium nitroprusside (100 µg) was followed 60 seconds later by a bolus injection of the vasoconstrictor phenylephrine hydrochloride (150 µg) to induce a fall and subsequent rise in arterial blood pressure of ~15 to 20 mm Hg below and above baseline. This sequence was repeated 3 times with 15 minutes of quiet rest between trials. The relation of R-R interval (ECG) to beat-by-beat systolic pressure (Finapres) during the pressure rise (from nadir to peak; an ascending pressure stimulus) provides a measure of baroreflex control of cardiac vagal outflow. R-R interval was regressed against 3 mm Hg systolic pressure ranges. Because the relationship between systolic pressure and R-R interval is sigmoidal18 and not linear, a 4-parameter sigmoid was fit to the data (TableCurve, Jandel Scientific) to calculate peak gain and the R-R interval operating range.18 Gain was also calculated by the standard approach, in which a straight line was regressed for the data points falling in the linear section of the curve between the threshold and saturation region.

**Integrated Baroreflex Assessment**

Graded LBNP was used to induce a gradual decline in central blood volume without the confounding effects of muscle contraction. Supine subjects were placed in a metal tank. A neoprene skirt was used to obtain an airtight seal at the waist. After a 5-minute baseline data collection period, negative pressures of –10, –20, –30, –40, and –50 mm Hg were generated. Although low-level LBNP (–10 and –20 mm Hg) is commonly used to isolate the cardiopulmonary baroreceptors, recent data indicate arterial baroreceptor involvement.19,20 Each stage lasted 5 minutes. Respiration (Respirtrace), R-R interval (ECG), beat-by-beat systolic blood pressure (Finapres), oscillometric blood pressure (Dinamap, Critikon Co), and forearm vascular resistance (FVR; mean arterial pressure divided by forearm blood flow, in arbitrary units) were recorded. Forearm blood flow was determined with a mercury-in-silastic strain gauge placed around the forearm. A rapid cuff inflator (D.E. Hokanson) was used to inflate and deflate the cuff. The volume of blood pooling in the lower extremity was estimated throughout the protocol by a previously placed strain gauge.

### Statistics

Data are expressed as mean±SEM. Unpaired t tests were used to compare responses between healthy controls and patients diagnosed with idiopathic orthostatic intolerance. A P level <0.05 was considered significant. A 2-way ANOVA (group, patients versus controls; time, levels of negative pressure) with repeated measures was used to evaluate low-level LBNP (–10 and –20 mm Hg) stages and all levels of LBNP (SAS statistical software, SAS Institute Inc). Preplanned comparisons were performed with unpaired t tests whenever the ANOVA detected a significant effect. Because the present investigation focused on autonomic cardiovascular control, data on cardiac chronotropy were analyzed and are reported by R-R interval. However, where appropriate, data were also analyzed by heart rate.

### Results

**Subject Characteristics**

Subject demographics can be found in Table 1. Data obtained from the questionnaires indicated that all patients diagnosed...
with idiopathic orthostatic intolerance reported symptoms of lightheadedness or dizziness with standing. All patients also reported fatigue as a major symptom. Other frequently reported symptoms included a rapid heart rate/palpitations (88%) and nausea (57%). Eighty-one percent (13/16) of the patients met the revised Centers for Disease Control and Prevention (CDC) criteria for a diagnosis of chronic fatigue syndrome (CFS).21 None of the healthy control subjects reported a regular occurrence of symptoms such as lightheadedness or fatigue.

**Plasma/Blood Volume and Venous Compliance**
Baseline plasma volume (38.0±1.4 versus 42.5±2.1 mL/kg, P=0.09) and blood volume (55.8±1.8 versus 63.2±3.1 mL/kg, P=0.054) tended to be lower in patients than controls. Hematocrit was similar (37.3±0.6 versus 38.0±1.1%, P=0.53), and venous compliance was lower in patients than in controls (2.5±0.2 versus 3.7±0.4 AU, P<0.05).

**Baseline Hemodynamic Assessment**
Baseline resting heart rate (76±3 versus 67±2 bpm, P=0.02) and mean arterial pressure (93±3 versus 82±2 mm Hg, P=0.009) were higher in patients. There were no differences in the maximum-minimum heart rate difference with deep respiration or the Valsalva ratio (see Table 1). There was a difference in the minimum heart rate achieved during the blood pressure rise of the Valsalva maneuver (phase IV), with patients having an attenuated slowing of heart rate compared with controls (see Table 1). There was also a trend (P=0.19) for patients to have a faster heart rate in response to the pressure fall during the Valsalva maneuver (see Table 1).

**Cardiac Vagal Baroreflex Sensitivity**
An example of the sigmoidal relationship between systolic pressure and R-R interval for a representative patient and control subject can be found in Figure 1. Cardiac vagal baroreflex gain with the modified Oxford technique was significantly lower (P≤0.01) in patients than in control subjects (see Figure 2). Patients also had a significantly lower gain when a straight line was regressed in the linear region of the systolic pressure–R-R interval relationship (data not shown). Similar differences were also noted in the heart rate–derived baroreflex gains (−1.6±0.3 versus −2.4±0.3 bpm/mm Hg, P≤0.05). There was a trend for the R-R interval operating range to be lower in patients (323±31 ms) than in controls (456±66 ms, P=0.09).

**Integrated Baroreflex Assessment**
LBNP data can be found in Table 2. Across all levels of negative pressure, there was a progressive shortening of R-R interval, a decline in arterial pressure, an increase in FVR, and an increase in calf circumference for patients and controls (ANOVA, P≤0.05). There was no change in respiration rate in patients and controls during the protocol. For low-level LBNP, the ANOVA detected a significant group (patients versus controls) effect for R-R interval, with patients having a significantly shorter R-R interval at the −10 and −20 mm Hg stage (Figure 3). The slope of the response between negative pressure applied and R-R interval was also steeper (more negative) in patients than in controls for the −10 and −20 mm Hg stage (−5.0 versus −2.2 ms/mm Hg). Because only 5 total subjects (4 patients and 1 control) were able to complete the −50 mm Hg stage (the others reported presyncopal symptoms along with a decline in blood pressure), the −50 mm Hg stage was not used in the statistical analysis. We also related the changes in R-R interval, heart rate, and FVR to changes in calf circumference and found no differences in slope (data not shown). However, marked intersubject and intrasubject variability in calf circumference precluded us from drawing a definitive conclusion based on these assessments. Although data are presented as R-R intervals, analyses were also performed with heart rate. Similar differences were found.

**Discussion**
Idiopathic orthostatic intolerance has become an increasingly recognized disorder, with patients typically complaining of lightheadedness, nausea, and fatigue when assuming the upright posture. These symptoms are associated with an exaggerated postural-induced tachycardia. The primary aim of the current study was to examine possible physiological correlates of idiopathic orthostatic intolerance. The major finding is that patients who present with symptoms of orthostatic intolerance have depressed cardiac vagal barore-
Baroreflex sensitivity. This difference in dynamic heart rate control does not appear to be related to deficits in vagal efferent activity, because respiratory-mediated vagal modulation of heart rate variability, as assessed by the maximum minus minimum heart rate difference, was not different in patients versus controls.

The present data differ from an earlier report in which it was concluded that baroreflex sensitivity is preserved in patients with chronic orthostatic intolerance. Importantly, however, those data revealed strong trends toward impaired cardiac vagal baroreflex sensitivity in the patient group, derived from both α-index (P<0.06 between groups) and steady-state vasoactive drug infusions (P<0.08 between groups). The impaired baroreflex gains are also consistent with a more recent report by the same group. The link between impaired cardiac vagal baroreflex sensitivity and orthostatic intolerance has been demonstrated previously in young healthy men after head-down bed rest, where low baroreflex sensitivity and a restricted R-R interval operating range (ie, buffer capacity) were associated with orthostatic hypotension. These data, however, are only partially applicable to the present study in that patients with idiopathic orthostatic intolerance are defined by a lack of significant orthostatic hypotension.

We also examined cardiovascular control during baroreflex disengagement utilizing lower-body suction as a descending pressure stimulus. At low levels of LBNP, we observed the R-R interval was significantly shorter in patients than in controls. For example, at the −20 mm Hg stage, patients had a 21% shorter R-R interval. Prior studies have used low levels of LBNP to isolate the cardiopulmonary reflex; however, more recent data suggest that there is also engagement of the arterial baroreflex, precluding the interpretation that this is a specific alteration in the cardiopulmonary reflex.

Taken together, these data indicate that the altered control of heart rate reported in this patient group may be due to arterial baroreflex dysfunction; that is, these patients are not able to properly slow heart rate in response to baroreflex engagement during an ascending pressure stimulus, which leads to an exaggerated tachycardia. Furthermore, impaired baroreflex function may be responsible for the increased central sympathetic outflow that has been reported in patients with chronic orthostatic intolerance and may be responsible in part for the postural tachycardia. It is of interest that the increased sympathetic outflow observed in both animal models and human studies of congestive heart failure is associated with and may be secondary to impaired baroreflex control.

In summary, whether an ascending or descending pressure stimulus is used, patients with idiopathic orthostatic intolerance respond with faster heart rates than healthy control subjects, which suggests differential gains. This is also supported by the minimum (P=0.05 between groups) and maximum (P=0.19 between groups) heart rates achieved during the pressure rise and fall of the Valsalva maneuver.

The pathophysiological basis of symptoms of orthostatic intolerance in the absence of hypotension is unknown. In the

### Figure 3.

Mean±SEM R-R interval responses to low levels of LBNP in patients and control subjects. ANOVA detected a significant group effect (P<0.05, patients vs controls) for R-R interval, and post hoc analysis revealed differences to be at the −10 and −20 mm Hg stages.

<table>
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<tr>
<th>TABLE 2. LBNP Data for Patients and Controls</th>
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MAP indicates mean arterial pressure.

Across all levels of LBNP, there was a progressive decline in R-R interval and MAP and an increase in both FVR and calf circumference for patients and controls (P<0.05, ANOVA). There was a group effect (patients vs controls) for R-R interval during low-level LBNP (P<0.05, ANOVA). Post hoc analysis revealed these differences to be at the −10 and −20 mm Hg stage (P<0.05, post hoc analysis).
present study, despite a similar physiological stress (a gradual decline in externally applied negative pressure, arterial pressure, and blood pooling), a qualitative assessment of symptoms during the LBNP protocol indicated that patients experienced more symptoms such as lightheadedness or dizziness than the healthy control subjects. This may suggest a more heightened sensitivity to a rapid heart rate in patients with idiopathic orthostatic intolerance. Although there are no reports that have assessed symptoms during rapid cardiac pacing in supine patients with orthostatic intolerance, the present data suggest that this patient group may respond adversely to an inappropriate tachycardia. The present data also appear to support the speculation that symptoms of orthostatic intolerance are elicited by central responses to the inappropriate tachycardia, and dysfunction within the baroreflex arc as a possible cause of the tachycardia.

Hypovolemia and increased venous compliance may contribute to orthostatic intolerance. Our data indicate that this group of patients had a 13% lower blood volume (P = 0.054) than their age-matched healthy counterparts. Jacob et al\textsuperscript{23} reported lower blood volume and a reduced plasma renin activity in a group of patients with orthostatic intolerance. Lower blood volume may cause a compensatory increase in sympathetic outflow, contributing to the suspected hyperadrenergic state previously reported in similar patients.\textsuperscript{7} Although the present data only indicate strong trends for differences in plasma and blood volume, hypovolemia may nonetheless play an important role in the pathogenesis of this disorder.

A previous study\textsuperscript{5} has drawn attention to the presence of increased venous derervation and pooling in patients with hyperadrenergic orthostatic hypotension. We hypothesized that patients with idiopathic orthostatic intolerance (without hypotension) would also have alterations in venous compliance. Against expectations, the present data indicate that patients had lower venous compliance than controls, indicating that this does not appear to play a contributing pathophysiological role. Two possibilities may explain this finding. First, increased sympathetic outflow to the venous system may result in a decrease in venous compliance.\textsuperscript{24} Alternatively, it is possible that incomplete venous drainage, due to excessive venous pooling before the compliance measurement was begun, left the patients at a higher starting point on the venous compliance curve. Although we used standard techniques for measuring venous compliance,\textsuperscript{15} this approach may not be suitable for patients with orthostatic intolerance. This issue merits further study.

A functional dysautonomia of the limbs causing vasoconstrictor failure has been suggested as a possible cause of orthostatic intolerance.\textsuperscript{5,4} Limb vasoconstriction during orthostatic stress has been used as an index of sympathetic function. In the present study, both patients and control subjects responded with an appropriate increase in FVR, providing no evidence of autonomic dysfunction of the upper limbs. We did not assess sympathetic vasoconstrictor function of the lower limbs during the LBNP protocol.

Symptoms of orthostatic intolerance are manifest in a broad spectrum of disorders. For example, this disorder is associated with the CFS, with some suggesting that orthostatic intolerance may contribute to the fatigue associated with CFS.\textsuperscript{25–27} The patients recruited for the current study had a diagnosis of idiopathic orthostatic intolerance, with most (13/16) also meeting the CDC criteria for a diagnosis of CFS.\textsuperscript{21} The high percentage (81%) of patients in the current study that meet the CDC definition for CFS makes these data unique. Chronic fatigue is a common complaint in patients with idiopathic orthostatic intolerance, and there appears to be considerable overlap between the 2 disorders. The current patient cohort also meets the commonly used diagnostic criteria for postural tachycardia syndrome.

There are several possible study limitations. Central venous pressure was not measured; instead, changes in calf circumference were used as a noninvasive index of blood pooling during LBNP. The amount of blood pooled during the protocol was not significantly different between groups. LBNP may not duplicate the stress of standing. This appears to be particularly true in the present study, because more patients than controls were able to complete the –50 mm Hg stage. However, as discussed, the patients responded at lower levels of LBNP with faster heart rates and more symptoms.

In summary, the present data indicate that arterial baroreflex function is altered in patients with idiopathic orthostatic intolerance, possibly contributing to the exaggerated tachycardia and symptoms of orthostatic intolerance.

Acknowledgments

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References

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