Raised Cerebrovascular Resistance in Idiopathic Orthostatic Intolerance
Evidence for Sympathetic Vasoconstriction

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Abstract—Patients with idiopathic orthostatic intolerance (IOI) exhibit symptoms suggestive of cerebral hypoperfusion and an excessive decrease in cerebral blood flow associated with standing despite sustained systemic blood pressure. In 9 patients (8 women and 1 man aged 22 to 48 years) with IOI, we tested the hypothesis that volume loading (2000 cc normal saline) and α-adrenoreceptor antagonism improve systemic hemodynamics and cerebral perfusion and that the decrease in cerebral blood flow with head-up tilt (HUT) could be attenuated by α-adrenoreceptor blockade with phentolamine. At 5 minutes of HUT, volume loading (−20±3.2 bpm) and phentolamine (−18±3.4 bpm) significantly reduced upright heart rate compared with placebo; the effect was diminished at the end of HUT. Phentolamine substantially increased upright heart rate at 5 minutes (20±3.7 bpm) and at the end of HUT (14±5 bpm). With placebo, mean cerebral blood flow velocity decreased by 33±6% at the end of HUT. This decrease in cerebral blood flow with HUT was attenuated by all 3 interventions. We conclude that in patients with IOI, HUT causes a substantial decrease in cerebrovascular blood flow velocity. The decrease in blood flow velocity with HUT can be attenuated with interventions that improve systemic hemodynamics and therefore decrease reflex sympathetic activation. Moreover, α-adrenoreceptor blockade also blunts the decrease in cerebral blood flow with HUT but at the price of deteriorated systemic hemodynamics. These observations may suggest that in patients with IOI, excessive sympathetic activity contributes to the paradoxical decrease in cerebral blood flow with upright posture. (Hypertension. 1998;32:699-704.)

Key Words: cerebral blood flow ■ receptors, adrenergic ■ phentolamine ■ phenylephrine ■ intolerance, orthostatic ■ tachycardia

Idiopathic orthostatic intolerance (IOI) is commonly defined as a >30 bpm increase in heart rate (HR) with standing associated with orthostatic symptoms but without significant orthostatic hypotension.1 The pathophysiology of this disorder, which mainly affects women in the second or third decade of life, is still imperfectly understood.2 It has been suggested that hypovolemia,3,4 excessive venous pooling in the lower extremities,5 partial dysautonomia involving the vasculature of the legs,6-8 or hypersensitivity of β-adrenoreceptors9,10 can contribute to the hemodynamic abnormalities of IOI. The unifying feature of patients with IOI is the presence of symptoms suggestive of cerebral hypoperfusion (eg, presyncope, visual changes, altered mentation) associated with standing despite largely sustained systemic arterial pressure. Recently, an excessive decrease in cerebral blood flow velocity with upright posture as well as stable mean arterial pressure (MAP) was reported in a single patient with a history and physical findings suggestive of IOI.11 Similarly, in a larger group of well-characterized IOI patients, mean middle cerebral blood flow velocity (mean MCAvel) decreased by 28% with 75° HUT; age- and gender-matched control subjects had only a 10% decrease in mean MCAvel.12 This substantial decrease in mean MCAvel despite a well-sustained MAP was associated with an increase in regional cerebrovascular resistance (CVR). We tested the hypothesis that volume loading and α-adrenoreceptor antagonism would improve systemic hemodynamics and cerebral perfusion in patients with IOI. Furthermore, we tested whether the increase in CVR with HUT could be prevented in part by α-adrenoreceptor blockade.

Subjects
We studied 9 patients with IOI (8 women and 1 man aged 22 to 48 years). They met the following criteria: (1) an increase in HR of at least 30 bpm within 5 minutes of standing without a concomitant decrease in systolic/diastolic blood pressure (BP) >20/10 mm Hg, (2) a plasma norepinephrine level of at least 600 pg/mL with standing, and (3) at least a 6-month history of typical symptoms of orthostatic intolerance (lightheadedness or dizziness, blurred vision, tremulousness, palpitations, chest discomfort, shortness of breath, nausea, or presyncope) with standing, which were significantly relieved by lying down. Subjects with systemic illnesses that could affect the autonomic nervous system (eg, diabetes mellitus, amyloid-
osis) were excluded. All studies were approved by the Vanderbilt Investigational Review Board, and subjects gave informed consent before the study.

Protocol
Patients were admitted to the Elliot V. Newman Clinical Research Center at Vanderbilt University Medical Center at least 2 days before the study. All subjects were placed on a 150-mEq sodium and 70-mEq potassium diet free of substances that could interfere with catecholamine measurements at least 3 days before testing. Medications were discontinued at least 5 half-lives before testing. Patients underwent autonomic evaluation including completion of a standardized questionnaire, determination of orthostatic vital signs, a battery of autonomic cardiovascular function tests, and plasma catecholamine determination supine and standing. Subjects then underwent a series of HUT tests in random order while receiving an intravenous infusion of phenylephrine, phentolamine, or placebo (normal saline) in a single-blinded fashion. Finally, patients underwent a HUT test after volume loading with normal saline. Infusions were given through an antecubital heparin lock. All blood samples were obtained by adding the scores for each symptom. Orthostatic symptoms, the most bothersome symptom was given a score of 10 and the least bothersome symptom a score of 1. A representative list of symptoms for the whole group of patients was obtained by adding the scores for each symptom.

Autonomic Evaluation
Patients completed a standardized questionnaire for the evaluation of autonomic symptoms. Patients were asked to choose from a list the 10 most bothersome symptoms. The most bothersome symptom was determined mainly for monitoring purposes. However, manual brachial BP was used for further analysis. The MCA was insonated through the temporal window using a 2-MHz probe (Pioneer, EMD). To estimate regional CVR, MAP was divided by mean MCAvel. Baseline measurements were taken after the subjects had been supine for at least 20 minutes. Then the drug infusions were begun or the subjects were volume loaded.

The placebo (normal saline) was adjusted to give a volume similar to that during phenylephrine or phentolamine infusion. The infusion rate of phenylephrine was increased until either HR decreased by 5 to 10 bpm or systolic BP increased by 5 to 10 mm Hg. Phentolamine was given as an initial bolus followed by a continuous infusion. Phentolamine bolus doses were repeated and the infusion rate was increased until either HR increased by 5 to 10 bpm or systolic BP decreased by 5 to 10 mm Hg. Placebo, phenylephrine, and phentolamine infusions were continued at a constant rate after the end points above were reached. Subjects were volume loaded while supine by administration of 2000 mL normal saline over 3 hours.

After steady-state infusion had been reached or volume loading was complete, patients were tilted to 75° HUT and remained at 75° HUT for 30 minutes or until symptoms occurred that prevented continuation of the study. Plasma catecholamine levels were determined at the end of HUT. Patients were then returned to 0° HUT, and drug infusions were continued for an additional 15 minutes.

Statistics
Data are expressed as mean±SEM. Intrainsividual and interindividual differences were analyzed by 2-tailed paired and unpaired t tests, respectively. If appropriate, ANOVA testing was used. A value of P<0.05 was considered statistically significant.

Results

Clinical Characteristics
The most bothersome symptom for most patients was excessive fatigue, followed by presyncope (Figure 1). Worsening of symptoms during menstruation was described by 57% of the women.

Autonomic Evaluation
After 3 minutes of standing, HR increased by 54±5 bpm. BP did not change with standing (Table). Plasma norepinephrine increased from 1.4±0.16 nmol/L (230±27 pg/mL) supine to 5.0±0.60 nmol/L (840±100 pg/mL) after 30 minutes of
standing \((P=0.0001)\). Plasma epinephrine increased from 0.29±0.15 nmol/L \((51±28\ \text{pg/mL})\) supine to 0.42±0.17 nmol/L \((77±31\ \text{pg/mL})\) after standing \((P<0.01)\). Patients had normal respiratory sinus arrhythmia and a normal Valsalva ratio consistent with intact parasympathetic efferents to the heart. At least partial integrity of sympathetic efferents was indicated by a normal handgrip test and a normal cold pressor response (Table).

**HUT With Transcranial Doppler**

Supine MAP and HR were 95±3 mm Hg and 75±3 bpm, respectively, before placebo infusion and did not change during the infusion (Figure 2). With HUT, HR substantially increased by 42±6 bpm after 5 minutes and further increased toward the end of HUT by 58±6 bpm above baseline \((P<0.001\text{ for both})\). MAP was 94±2 mm Hg immediately before HUT and was maintained after 5 minutes of HUT \((92±4)\) mm Hg. At the end of HUT, MAP decreased to 81±10 mm Hg \((P<0.05)\). With placebo, mean MCA\(_{\text{int}}\) decreased by 12±3% after 5 minutes of HUT \((P<0.05)\) (Figure 3, top). At the end of the tilt test, mean MCA\(_{\text{int}}\) was decreased by 53±6% \((P<0.001)\). CVR increased from 1.32±0.07 mm Hg \(\cdot s^{-1} \cdot \text{cm}^{-1}\) immediately before HUT to 1.7±0.1 mm Hg \(\cdot s^{-1} \cdot \text{cm}^{-1}\) at the end of HUT (Figure 3, bottom).

All patients underwent HUT with phenylephrine infusion; 8 patients underwent HUT after volume loading, and 7 patients underwent HUT with phentolamine. The durations of the tilt tests with phenylephrine infusion, volume loading, and phentolamine infusion were 30±0, 30±0, and 21±4 minutes, respectively. With placebo, the duration of the tilt test was 28±2 minutes. With phenylephrine infusion \((0.64±0.06\ \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1})\), supine MAP increased from 93±4 to 102±4 mm Hg. This increase in MAP was associated with a decrease in HR from 74±2 to 64±3 bpm. With phentolamine \((0.25±0\ \text{mg bolus}, 66.7±0\ \mu\text{g/kg continuous infusion})\), supine MAP did not change. There was no significant change in supine MAP or HR with volume loading. Supine HR, however, increased from 72±3 to 86±4 bpm with phentolamine.

After 5 minutes of HUT or at the end of HUT, no significant differences in MAP were detected with phenylephrine infusion, volume loading, or phentolamine infusion compared with placebo. Compared with placebo, phenylephrine infusion and volume loading blunted the increase in upright HR at 5 minutes of HUT by 18±3 and 20±3 bpm \((P<0.001)\), respectively (Figure 4). In contrast, with phentolamine the HR at 5 minutes of HUT was 20±4 bpm greater than with placebo \((P<0.01)\). At the end of HUT, there was no significant difference in HR among placebo, volume loading, or phenylephrine infusion, but HR was still 14±4 bpm.
greater than placebo with phentolamine infusion ($P<0.05$) (Figure 4).

None of the interventions significantly changed MCA$_{vel}$ in the supine position. At 5 minutes of HUT, there was no difference in mean MCA$_{vel}$ between any of the 3 interventions and placebo (Figure 5). At the end of HUT, however, phenylephrine infusion, volume loading, and phentolamine infusion attenuated the decrease in mean MCA$_{vel}$ with upright posture (for all, $P<0.05$) (Figure 5). At the end of HUT, volume loading significantly blunted the increased regional CVR (1.44±0.10 mm Hg · s$^{-1}$ · cm$^{-1}$ with volume loading, 1.70±0.10 mm Hg · s$^{-1}$ · cm$^{-1}$ with placebo; $P<0.05$) (Figure 6). There was a trend for phenylephrine to decrease regional CVR at the end of HUT (1.53±0.13 mm Hg · s$^{-1}$ · cm$^{-1}$ with phenylephrine, 1.70±0.10 mm Hg · s$^{-1}$ · cm$^{-1}$ with placebo; $P=0.1$). With phentolamine, there was a decrease in regional CVR toward the end of HUT compared with placebo that was borderline in significance (1.48±0.11 mm Hg · s$^{-1}$ · cm$^{-1}$ with phentolamine, 1.66±0.10 mm Hg · s$^{-1}$ · cm$^{-1}$ with placebo; $P=0.06$).

Blood samples during HUT could not be obtained in all patients, seemingly because of peripheral vasoconstriction. Therefore, plasma norepinephrine levels with volume loading could not be analyzed because the sample size was too small. With phenylephrine infusion, upright norepinephrine levels at the end of HUT were significantly smaller than they were with placebo (3.2±0.37 nmol/L [537±62 pg/mL] with phenylephrine, 4.3±0.44 nmol/L [734±74 pg/mL] with placebo, $n=6$; $P<0.01$) (Figure 7). With phentolamine infusion, upright norepinephrine levels at the end of HUT were significantly greater than they were with placebo (8.3±0.64 nmol/L [1407±108 pg/mL] with phenylephrine, 4.5±0.38 nmol/L [758±65 pg/mL] with placebo, $n=6$; $P<0.01$) (Figure 7).

**Discussion**

The main novel finding of this study is that both volume loading and infusion of an $\alpha$-adrenoreceptor agonist attenuate the decrease in mean MCA$_{vel}$ with HUT in patients with IOI.
The decrease in mean MCA vel could be caused by a decrease in MAP. Because with these interventions there was no increase in MAP, the change in cerebrovascular tone. The decrease in upright HR and BP, that can be used to obtain objective treatment outcomes in IOI. Furthermore, new strategies for the treatment of this condition that selectively target the cerebral circulation could be developed.

The main limitation of this study is that in patients with IOI, the degree of impairment of cerebral perfusion cannot be extrapolated from BP and HR data. Therefore, cerebral blood flow is an important variable, independent of HR and BP, that can be used to obtain objective treatment outcomes in IOI. Furthermore, new strategies for the treatment of this condition that selectively target the cerebral circulation could be developed.

The decrease in blood flow velocity with HUT can be attenuated with interventions that improve systemic hemodynamics and therefore decrease reflex sympathetic activation. Moreover, α-adrenoceptor blockade also blunts the decrease in cerebral blood flow with HUT but at the price of deteriorated systemic hemodynamics. These observations suggest that in patients with IOI, excessive sympathetic activity contributes to the paradoxical decrease in cerebral blood flow with upright posture.

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Paradoxically, α-adrenoceptor blockade with phenolamine also blunted the decrease in mean MCA vel despite a substantial worsening in systemic hemodynamics. The improvement in regional cerebrovascular perfusion with these interventions appeared to be due in part to a decrease in CVR.

Patients with IOI characteristically have symptoms suggestive of cerebral hypoperfusion with upright posture even in the absence of orthostatic hypotension. Furthermore, IOI patients have a greater decrease in mean MCA vel than normal control subjects with graded HUT. This excessive decrease in mean MCA vel is associated with an excessive increase in regional CVR. In the present study, we observed a similar decrease in mean MCA vel in IOI patients with HUT. The decrease in mean MCA vel could be caused by a decrease in MAP, an increase in CVR, or a combination of these 2 mechanisms. Toward the end of HUT, patients exhibited a significant decrease in MAP. The normal response to a decrease in MAP would be a compensatory decrease in CVR. Instead, we found a marked increase in CVR at the end of HUT.

Oral α-adrenergic agonist (midodrine) and volume loading blunt the upright tachycardia and ameliorate symptoms in IOI patients, at least in the first 5 minutes of standing. In the present study, α-adrenoceptor agonism (intravenous phenylephrine) and volume loading not only attenuated the HR increase with HUT but also lessened the decrease in mean MCA vel. Because with these interventions there was no change in MAP, which is presumably the main determinant of cerebral perfusion pressure under the given experimental conditions, the change in cerebral perfusion must be due to a change in cerebrovascular tone. The decrease in upright HR with volume loading and phenylephrine infusion and the decrease in upright plasma norepinephrine with phenylephrine infusion are consistent with a decrease in sympathetic tone. Moreover, phenylephrine infusion significantly decreased upright norepinephrine. These observations, however, do not permit distinction between improvement in cerebral blood flow due to a decrease in reflex sympathetic activation or some alternative mechanism.

In contrast to the effects of volume loading and phenylephrine infusion, phenolamine infusion substantially worsened systemic hemodynamics, as shown by the profound increase in upright HR. Furthermore, there was a dramatic increase in upright plasma norepinephrine with phenolamine, presumably caused by reflex sympathetic activation in response to blockade of vascular α-adrenoceptors and perhaps also by α2-adrenoceptor–mediated norepinephrine release. Despite worsened hemodynamics, mean MCA vel decreased significantly less with phenolamine than it did with placebo at the end of HUT. One possible explanation for these observations is that blockade of vascular α-adrenoceptors in the brain attenuates sympathetically mediated vasoconstriction.

Particularly appealing is the hypothesis that the constriction of cerebral blood vessels leading to the increase in CVR is sympathetically mediated. Many of the symptoms that patients with IOI commonly experience with standing (eg, tachycardia, diaphoresis) are suggestive of excessive sympathetic activation, and plasma norepinephrine is increased in these patients, especially with standing. It is probable that in these patients, this sympathetic activation is reflexively mediated to compensate for excessive venous pooling with standing compounded by hypovolemia. While this sympathetic activation may be of appropriate intensity to preserve systemic hemodynamics, it may be inappropriately excessive in the local environment of the cerebral blood vessels, resulting in the observed symptoms. An alternative explanation is a primary hyperadrenergic state that could secondarily lead to hypovolemia and orthostatic intolerance.

One important implication of this study is that in patients with IOI, the degree of impairment of cerebral perfusion cannot be extrapolated from BP and HR data. Therefore, cerebral blood flow is an important variable, independent of HR and BP, that can be used to obtain objective treatment outcomes in IOI. Furthermore, new strategies for the treatment of this condition that selectively target the cerebral circulation could be developed.

The main limitation of this study is the method used to assess cerebral perfusion. Transcranial Doppler is the only readily available method to detect acute changes in cerebral perfusion. However, it measures cerebral blood flow velocity rather than cerebral blood flow. Because blood flow velocity is directly related to blood flow only if the diameter of the insonated blood vessel remains constant, a moderate change in vessel diameter would translate into a substantial change in blood flow. It has been shown that the diameter of the MCA changes little with hemodynamic perturbations.

We conclude that in patients with IOI, HUT causes a substantial decrease in cerebrovascular blood flow velocity. The decrease in blood flow velocity with HUT can be attenuated with interventions that improve systemic hemodynamics and therefore decrease reflex sympathetic activation. Moreover, α-adrenoceptor blockade also blunts the decrease in cerebral blood flow with HUT but at the price of deteriorated systemic hemodynamics. These observations suggest that in patients with IOI, excessive sympathetic activity contributes to the paradoxical decrease in cerebral blood flow with upright posture.
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