Research Paper

Clinical Autonomic Research 2000, **10:**29–33

Hemodynamic and symptomatic effects of acute interventions on tilt in patients with postural tachycardia syndrome

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Received February 16, 1999; accepted as revised October 19, 1999

A variety of approaches have been used to alleviate symptoms in postural tachycardia syndrome (POTS). Drugs reported to be of benefit include midodrine, propranolol, clonidine, and phenobarbital. Other measures used include volume expansion and physical countermaneuvers. These treatments may influence pathophysiologic mechanisms of POTS such as α-receptor dysfunction, β-receptor supersensitivity, venous pooling, and brainstem center dysfunction. The authors prospectively studied hemodynamic indices and symptom scores in patients with POTS who were acutely treated with a variety of interventions. Twenty-one subjects who met the criteria for POTS were studied (20 women, 1 man; mean age, 28.7 ± 6.8 y; age range, 14–39 y). Patients were studied with a 5-minute head-up tilt protocol, ECG monitoring, and noninvasive beat-to-beat blood pressure monitoring, all before and after the administration of an intervention (intravenous saline, midodrine, propranolol, clonidine, or phenobarbital). The hemodynamic indices studied were heart rate (ECG) and systolic, mean, and diastolic blood pressure. Patients used a balanced verbal scale to record any change in their symptoms between the tilts. Symptom scores improved significantly after the patients received midodrine and saline. Midodrine and propranolol reduced the resting heart rate response to tilt ($p < 0.005$) and the immediate and 5-minute heart rate responses to tilt ($p < 0.002$). Clonidine accentuated the immediate decrease in blood pressure on tilt up ($p < 0.05$). It was concluded that midodrine and intravenous saline are effective in decreasing symptoms on tilt in patients with POTS when given acutely. Effects of treatments on heart rate and blood pressure responses generally reflected the known pharmacologic mechanisms of the agents.

Key words: POTS, treatment, midodrine, saline, β-blocker.

In recent years, postural tachycardia syndrome (POTS) has been increasingly recognized as a common cause of potentially disabling orthostatic symptoms. Symptoms may include dizziness, blurred vision, fatigue, weakness, palpitations, anxiety, tremulousness, diaphoresis, gastrointestinal symptoms, and vasomotor symptoms. While the etiology of these symptoms is complex and not well understood, brain hypoxia and overactivation of components of the sympathetic nervous system are believed to play major roles in their generation.

The pathophysiology of POTS is uncertain. Proposed mechanisms include hypovolemia [1–3], venous pooling [4,5], α-adrenergic receptor dysfunction [6], β-adrenergic receptor supersensitivity [7], altered sympathetic–parasympathetic balance [8], and brainstem dysregulation [7].

Current treatment modalities are directed at the mechanisms demonstrated or thought to be active in particular patients. Commonly used approaches include volume expansion salt ± water supplementation, midodrine α-agonist, propranolol β-blockers, clonidine α_2-agonist, and phenobarbital central action.

This study was performed to evaluate the hemodynamic and symptomatic effects of some commonly used POTS treatments in patients who met the POTS criteria. We also sought correlations between symptomatic and hemodynamic effects of the intervention. A preliminary report has been published previously [9].

Methods

Patients

All of the following conditions were required for diagnosis of POTS: 1) an increase of at least 30 beats per minute in the heart rate within 5 minutes on standard head-up tilt (to 80°) or on active standing; 2) consistent symptoms of cerebral hypoperfusion on head-up tilt or on active standing that clear upon lying down; 3) absence of orthostatic hypotension; and 4) absence of any concurrent illness, systemic illness, or autonomic disorder known to cause orthostatic intolerance.

We studied 21 patients who met the criteria for POTS (20 females, 1 male; mean age ± standard error of mean, 29.3 ± 1.4 y; age range, 14–39 y). Patients refrained from taking any medications for at least 72 hours before each day of the study. All experimental procedures were approved by the institutional review board.

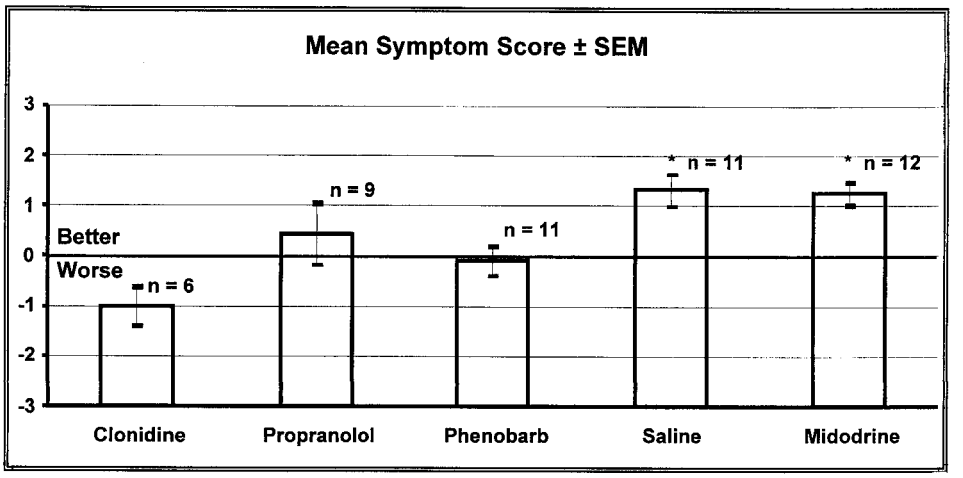

Figure 1. Symptom scores reported by patients comparing their ability to perform the orthostatic activities after the intervention. Figure shows mean scores ± standard error of the mean. Saline and midodrine showed significant differences, $p < 0.05$.

Head-up tilt study

Each pair of tilt studies (control and intervention) was carried out on a separate day in the morning. Different interventions were done either on consecutive days or 2 to 3 days apart. Each study consisted of a pair of tilts. After a supine baseline period of at least 5 minutes, the patients were passively tilted to 80° for at least 5 minutes, followed by a post-tilt rest.

The first tilt was performed as a baseline. The patient then received medication or intravenous saline. One hour after taking the medication or immediately after completion of saline infusion, a second tilt was performed. Hemodynamic parameters were monitored during each tilt. The parameters monitored were heart rate (ECG) and systolic, mean, and diastolic blood pressures (Finapres; Ohmeda Monitoring Systems, Englewood, CO, USA).

Interventions

We studied the effects of five interventions, given orally except for intravenous normal saline. Patients were given midodrine (10 mg), intravenous normal saline (1,000 ml), propranolol (40 mg), clonidine (200 μg), or phenobarbital (120 mg). After the administration of the treatment and a time interval of 68 ± 17 minutes for oral medications, a second tilt was performed. Medication dosages were chosen to be sufficient so that an acute effect of a single dose could be expected to have a measurable symptomatic and hemodynamic effect without being so high as to be inapplicable to clinical practice. Each patient underwent an average of three interventions.

Data collection, processing, and analysis

Hemodynamic parameters were collected on a beat-to-beat basis using microcomputer-based data acquisition packages (custom-written software; Snapmaster, HEM Data Corp., Southfield, MI, USA). The resulting data were saved in permanent storage for off-line analysis. To allow meaningful numerical comparisons between hemodynamic parameters from different tilts, we decided to reduce the beat-to-beat data by defining five standard epochs for each tilt and using the average values for each epoch for between-tilt comparisons. Each epoch was 30 seconds long, beginning at 2 minutes before tilt, immediately after tilt up, 2 minutes after tilt up, 5 minutes after tilt up, and 2 minutes after tilt back. The epochs were chosen to represent baseline status, immediate hemodynamic changes on tilt up, changes on continued tilt, and the return to baseline status.

Changes in the measured parameters within each tilt were tested with use of the Student *t* test. When testing the effects of the interventions, averaged control tilt data for each of the five epochs (time points) were paired with the postintervention tilt data for the corresponding time point. Statistical comparisons between the epoch averages for the control tilts and treated tilts for each parameter were performed using the Mann-Whitney U test. P values less than 0.05 were accepted as significant for both tests.

After each pair of tilts, the subjects were asked to rate whether they had been able to perform their orthostatic activities more effectively after the intervention. A balanced 7-point verbal scale from -3 to +3 [10] was used (-3, much worse; -2, moderately worse; -1, mildly worse; 0, no

Table 1. Pooled control hemodynamic parameters

Units	Baseline	Immediate	2 Minutes	5 Minutes	After
HR, bpm	83.1 ± 2.1	114.3 ± 3.3	113.8 ± 3.0	117.8 ± 3.1	78.3 ± 2.1
SBP, mm Hg	125.1 ± 2.0	123.7 ± 3.3	127.9 ± 3.1	123.2 ± 3.4	125.7 ± 1.8
MBP, mm Hg	86.4 ± 1.8	93.0 ± 2.7*	97.0 ± 2.7*	94.8 ± 3.0*	88.1 ± 1.8
DBP, mm Hg	67.6 ± 1.8	78.1 ± 2.6*	82.1 ± 2.6*	81.2 ± 3.0*	69.8 ± 1.9

$n = 61$; mean ± SEM.
HR = heart rate; bpm = beats per minute; SBP = systolic blood pressure; MBP = mean blood pressure; DBP = diastolic blood pressure.
*$p < 0.05$ vs baseline.

Table 2. Midodrine hemodynamic parameters

	Baseline		Immediate		2 Minutes		5 Minutes		After	
Units	Control	Treated	Control	Treated	Control	Treated	Control	Treated	Control	Treated
HR, bpm	78.1 ± 3.6	66.8 ± 3.1	110.5 ± 7.0	103.3 ± 6.8	111.2 ± 6.1	107.3 ± 6.9	115.4 ± 6.2	111.3 ± 7.1	74.3 ± 3.8	62.2 ± 2.6
	n = 16, p = 0.000		n = 16, p = 0.028		n = 16, p = 0.198		n = 15, p = 0.146		n = 16, p = 0.001	
HP	796.1 ± 41.2	930.7 ± 46.6	570.6 ± 30.5	618.2 ± 38.6	563.8 ± 29.9	592.1 ± 35.3	542.2 ± 30.3	568.2 ± 33.2	843.0 ± 46.5	991.8 ± 44.1
	n = 16, p = 0.000		n = 16, p = 0.017		n = 16, p = 0.086		n = 15, p = 0.038		n = 16, p = 0.000	
SBP, mm Hg	124.9 ± 2.5	127.2 ± 2.6	123.1 ± 5.4	119.0 ± 6.3	130.8 ± 4.4	120.7 ± 6.1	123.9 ± 5.0	117.5 ± 6.1	125.7 ± 2.3	123.0 ± 3.6
					n = 16, p = 0.005					
MBP, mm Hg	88.1 ± 2.3	86.8 ± 2.4	94.6 ± 4.4	88.2 ± 5.4	100.7 ± 4.1	91.3 ± 5.1	96.6 ± 4.6	89.7 ± 5.1	88.7 ± 2.5	84.4 ± 2.9
					n = 16, p = 0.005		n = 15, p = 0.088			
DBP, mm Hg	70.2 ± 2.6	67.2 ± 2.6	80.9 ± 4.2	73.3 ± 5.1	86.2 ± 4.1	77.1 ± 4.7	83.5 ± 4.6	76.4 ± 4.7	70.6 ± 2.8	65.5 ± 2.9
			n = 16, p = 0.059		n = 16, p = 0.008		n = 15, p = 0.065		n = 16, p = 0.069	

Mean ± SEM.
HR = heart rate; bpm = beats per minute; HP = heart period; SBP = systolic blood pressure; MBP = mean blood pressure; DBP = diastolic blood pressure.

change; +1, mildly improved; +2, moderately improved; +3, much improved). Because the symptom scores were not necessarily normally distributed, we chose to use the nonparametric Mann-Whitney rank sum test for statistical comparisons, accepting p values less than 0.05 as significant. All statistics were computed with use of SYSTAT 7.0 for Windows (SPSS, Inc., Chicago, IL, USA).

Results

Symptom scores

Symptom scores (Fig. 1) were significantly higher than 0 (indicating an improvement in orthostatic symptoms after the intervention) for the saline- and midodrine-treated groups ($p < 0.05$), but not for the groups treated with other interventions. Scores for the propranolol- and clonidine-treated groups had a tendency to be greater than and less than 0, respectively, but the p value did not achieve significance.

Hemodynamic parameters

Baseline tilts. Pooled results of the 62 baseline tilts are presented in Table 1. The mean pre-tilt control heart rate was 79.7 beats per minute, whereas the mean heart rate at 5 minutes after tilt was 113.1 beats per minute. The systolic blood pressure did not change during baseline tilts, but there was a significant rise in the diastolic blood pressure.

Postintervention tilts. Results of the postintervention tilts are presented in Tables 2 through 6. The statistically significant differences in hemodynamic parameters between the post-treatment tilts and their corresponding control tilts were primarily confined to heart rate. Most of the observed effects were in keeping with expected pharmacologic actions of the drugs used.

Midodrine. The patients treated with midodrine had a lower heart rate at the pre-tilt epoch, at the immediate post-tilt epoch, and at the 5-minute epoch. The diastolic blood pressure was marginally lower at the immediate post-tilt epoch in postmidodrine tilts. At the 2-minute epoch, both systolic and diastolic blood pressure were lower in the postmidodrine tilts.

Saline. Saline infusion reduced heart rate during supine rest and head-up tilts, reaching statistical significance at the 2-minute mark in the saline-treated tilts. There were no differences in systolic or diastolic blood pressures after treatment with intravenous saline.

Propranolol. Propranolol treatment resulted in a significant decrease in heart rate at all time points. There were no differences in blood pressure between baseline and postpropranolol tilts.

Clonidine. Subjects treated with clonidine showed a significant post-tilt bradycardia. There was a significant increase in the immediate drop in systolic and diastolic blood pressure on tilt. Systolic and diastolic blood pressures continued to

Table 3. Saline hemodynamic parameters

	Baseline		Immediate		2 Minutes		5 Minutes		After	
Units	Control	Treated	Control	Treated	Control	Treated	Control	Treated	Control	Treated
HR, bpm	82.7 ± 4.8	79.7 ± 4.0	109.5 ± 4.6	104.5 ± 5.1	110.8 ± 5.2	103.1 ± 5.6	112.2 ± 5.8	108.5 ± 6.0	76.1 ± 5.1	75.3 ± 4.8
	n = 14, p = 0.097		p = 0.146		p = 0.008		p = 0.328		p = 0.736	
HP	759.3 ± 45.7	777.4 ± 37.5	562.3 ± 26.9	591.3 ± 27.4	557.1 ± 26.1	601.5 ± 28.9	552.3 ± 28.8	571.8 ± 29.3	834.3 ± 53.5	834.4 ± 46.5
	n = 14, p = 0.291		n = 14, p = 0.120		n = 14, p = 0.007		n = 13, p = 0.267		n = 14, p = 0.997	
SBP, mm Hg	125.4 ± 4.9	126.3 ± 3.8	122.1 ± 7.7	123.1 ± 6.1	127.4 ± 7.0	123.3 ± 6.2	121.3 ± 7.3	119.9 ± 6.0	120.9 ± 4.3	126.7 ± 4.1
MBP, mm Hg	87.0 ± 4.4	86.3 ± 2.8	91.1 ± 6.0	90.4 ± 4.7	96.1 ± 5.9	91.6 ± 4.9	92.6 ± 6.9	89.3 ± 4.8	83.6 ± 3.9	86.5 ± 3.1
DBP, mm Hg	68.2 ± 4.6	66.7 ± 2.7	76.1 ± 5.5	74.6 ± 4.1	81.0 ± 5.6	76.2 ± 4.4	78.8 ± 6.9	74.5 ± 4.4	65.4 ± 4.0	66.8 ± 2.8

Mean ± SEM.
HR = heart rate; bpm = beats per minute; HP = heart period; SBP = systolic blood pressure; MBP = mean blood pressure; DBP = diastolic blood pressure.

Table 4. Propranolol hemodynamic parameters

	Baseline		Immediate		2 Minutes		5 Minutes		After	
Units	Control	Treated	Control	Treated	Control	Treated	Control	Treated	Control	Treated
HR, bpm	87.1 ± 5.3	71.8 ± 5.0	117.0 ± 6.0	87.2 ± 4.9	117.6 ± 7.5	88.6 ± 4.8	117.1 ± 5.9	89.0 ± 4.8	84.8 ± 5.4	70.4 ± 4.6
	p = 0.001		p = 0.001		p = 0.001		p = 0.0002		p = 0.001	
HP	719.1 ± 50.9	875.3 ± 60.1	527.1 ± 28.1	708.8 ± 38.3	531.0 ± 33.4	696.0 ± 35.2	526.9 ± 28.6	693.7 ± 36.7	742.0 ± 55.9	891.5 ± 62.3
	n = 11, p = 0.002		*n* = 11, p = 0.001		*n* = 11, p = 0.000		*n* = 11, p = 0.000		*n* = 11, p = 0.001	
SBP, mm Hg	124.1 ± 4.5	122.9 ± 3.3	122.5 ± 6.3	115.0 ± 7.1	122.9 ± 8.1	118.8 ± 6.9	122.9 ± 7.9	115.9 ± 7.1	126.2 ± 4.2	117.9 ± 4.8
									n = 11, p = 0.048	
MBP, mm Hg	83.3 ± 3.8	84.7 ± 2.5	88.6 ± 5.2	85.8 ± 5.1	89.7 ± 6.3	89.5 ± 4.9	92.0 ± 6.1	87.9 ± 5.2	86.9 ± 3.8	83.3 ± 3.5
DBP, mm Hg	63.5 ± 4.1	66.2 ± 2.4	72.2 ± 5.1	71.8 ± 4.5	73.6 ± 5.7	75.3 ± 4.2	77.0 ± 5.5	74.5 ± 4.4	67.8 ± 3.9	66.5 ± 3.0

Mean ± SEM.
HR = heart rate; bpm = beats per minute; HP = heart period; SBP = systolic blood pressure; MBP = mean blood pressure; DBP = diastolic blood pressure.

be lower than control values at the 2-minute epoch but were unchanged at later epochs.

Phenobarbital. There were no differences in heart rate or blood pressure profiles between pretreatment and posttreatment tilts in the phenobarbital-treated group.

Discussion

The main findings of the present study are that volume expansion (with saline infusion) and the directly acting α-agonist midodrine significantly improved symptoms, and these agents and the β-receptor antagonist reduced the orthostatic tachycardia.

A 1-L volume expansion in the form of intravenous normal saline improved tilt tolerance, evaluated using a balanced validated scale [10], and reduced resting heart rate and orthostatic heart rate. This improvement in symptoms lends some support to the explanation for the previously described hypovolemia in POTS [2,3]. However, normovolemia with excessive venous pooling has also been reported [11], and an alterative explanation is that the volume expansion counteracts venous pooling [12].

The α-agonist midodrine improved tilt tolerance and attenuated the tachycardia of POTS. POTS has been suggested to be a limited autonomic neuropathy [13] because approximately 50% of patients develop the disorder after a presumed viral infection and show peripheral denervation on sudomotor tests, and the Valsalva maneuver is often characterized by a loss of late phase II, which is suggestive of peripheral adrenergic denervation [7]. More direct evidence of peripheral adrenergic denervation has been reported. Peripheral veins show denervation supersensitivity of infused α-agonists [11,14] and norepinephrine spillover is lower in the lower extremeties than in the upper extremities [15]. The response to midodrine lends support to the role of denervation in the pathophysiology of POTS.

Despite being commonly used as a treatment for POTS, 40 mg propranolol as a single dose did not have a significant symptomatic benefit in this acute setting. The expected significant bradycardia was observed, suggesting that the symptomatic improvement seen in long-term β-blocker treatment may not be due solely to its effects on heart rate. Clinical observation is that propranolol in low doses, typically 10 mg three times a day, is beneficial, whereas larger doses may result in excessive tiredness [7]. The assumption has been that the tachycardia is partly compensatory and partly a manifestation of β-receptor supersensitivity. A small dose might correct the supersensitivity, whereas a larger dose might block the beneficial compensatory response.

None of the other interventions had a significant effect on tilt tolerance, although clonidine showed a nonsignificant tendency to decrease tilt tolerance. The lack of strong effects for phenobarbital and clonidine does not preclude a beneficial effect with long-term dosing. The mechanism of action of phenobarbital is uncertain. If its action is similar to that of other anticonvulsants, benefits may be delayed. These findings are in overall agreement with a recent publication [1] reporting that the main change was in heart rate.

Table 5. Clonidine hemodynamic parameters

	Baseline		Immediate		2 Minutes		5 Minutes		After	
Units	Control	Treated	Control	Treated	Control	Treated	Control	Treated	Control	Treated
HR, bpm	89.7 ± 4.8	79.9 ± 3.8	124.7 ± 11.1	124.0 ± 8.9	127.5 ± 10.8	129.2 ± 8.9	135.1 ± 11.3	128.9 ± 9.5	82.3 ± 4.5	70.3 ± 4.2
	n = 7, p = 0.049		p = 0.886		p = 0.801		*n* = 6, p = 0.481		*n* = 7, p = 0.006	
HP	681.3 ± 37.8	763.6 ± 43.9	504.4 ± 44.2	498.3 ± 33.4	492.8 ± 44.4	477.0 ± 30.8	464.4 ± 48.9	478.3 ± 35.0	743.6 ± 43.2	873.0 ± 55.4
	n = 7, p = 0.082		*n* = 7, p = 0.771		*n* = 7, p = 0.569		*n* = 6, p = 0.662		*n* = 7, p = 0.008	
SBP, mm Hg	130.4 ± 9.8	121.9 ± 6.5	128.2 ± 12.0	105.7 ± 6.5	128.6 ± 13.3	113.7 ± 7.2	126.4 ± 17.1	113.4 ± 12.2	133.6 ± 8.0	126.1 ± 8.3
			n = 7, p = 0.035		*n* = 7, p = 0.071					
MBP, mm Hg	90.7 ± 8.2	86.0 ± 6.4	96.8 ± 10.9	81.5 ± 6.6	100.5 ± 12.5	88.1 ± 6.7	100.6 ± 16.9	86.2 ± 9.8	96.1 ± 9.2	90.1 ± 7.3
	n = 7, p = 0.215		*n* = 7, p = 0.041							
DBP, mm Hg	71.4 ± 7.9	68.5 ± 6.6	81.5 ± 10.5	69.9 ± 6.7	86.9 ± 12.3	75.8 ± 6.4	88.2 ± 17.2	73.2 ± 8.6	77.9 ± 9.9	72.6 ± 7.0
			n = 7, p = 0.054							

Mean ± SEM.
HR = heart rate; bpm = beats per minute; HP = heart period; SBP = systolic blood pressure; MBP = mean blood pressure; DBP = diastolic blood pressure.

Table 6. Phenobarbital hemodynamic parameters

	Baseline		Immediate		2 Minutes		5 Minutes		After	
Units	Control	Treated	Control	Treated	Control	Treated	Control	Treated	Control	Treated
HR, msec	82.8 ± 4.9	77.8 ± 4.1	116.2 ± 9.2	104.7 ± 5.5	109.8 ± 5.7	108.0 ± 5.6	118.7 ± 7.2	110.9 ± 5.7	78.1 ± 4.8	75.8 ± 4.9
	p = 0.074		p = 0.125		p = 0.528		p = 0.081		p = 0.340	
HP	760.1 ± 51.9	797.7 ± 42.8	548.8 ± 36.1	592.6 ± 31.3	564.6 ± 29.9	573.2 ± 29.1	528.0 ± 34.4	556.3 ± 28.1	809.8 ± 57.0	834.4 ± 56.2
	n = 13, p = 0.108		*n* = 13, p = 0.062		*n* = 13, p = 0.505		*n* = 12, p = 0.119		*n* = 13, p = 0.243	
SBP, mm Hg	122.9 ± 4.2	123.1 ± 3.4	124.7 ± 8.5	123.2 ± 7.2	128.6 ± 6.7	126.4 ± 7.4	123.2 ± 7.2	121.4 ± 6.9	126.3 ± 2.7	122.6 ± 3.7
MBP, mm Hg	84.1 ± 3.2	86.4 ± 3.0	94.6 ± 7.0	94.3 ± 6.6	97.8 ± 5.0	96.8 ± 6.1	94.8 ± 5.6	92.8 ± 5.6	88.9 ± 2.7	86.5 ± 3.1
DBP, mm Hg	65.3 ± 3.0	68.5 ± 3.1	80.0 ± 6.3	80.3 ± 6.5	83.0 ± 4.4	82.5 ± 5.7	81.1 ± 5.0	78.9 ± 5.2	70.7 ± 3.0	69.0 ± 3.0

Mean ± SEM.
HR = heart rate; HP = heart period; SBP = systolic blood pressure; MBP = mean blood pressure; DBP = diastolic blood pressure.

Acknowledgments

This study was supported in part by the National Institute of Neurological Disorders and Stroke (PO1 NS32352), Mayo GCRC Grant (M01 RR00585), National Aeronautics and Space Administration, and Mayo funds.

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