Neurocirculatory Abnormalities in Chronic Orthostatic Intolerance

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Background—Chronic orthostatic intolerance (COI) occurs in postural tachycardia syndrome (POTS) and in some individuals with repeated neurocardiogenic syncope/presyncope (NCS), without POTS. This study addressed whether patients with COI and POTS or NCS have neurocirculatory abnormalities during supine rest.

Methods and Results—Adult patients referred for COI who had POTS \( (n = 90, \text{mean} \pm \text{SEM} \text{age} 40 \pm 1 \text{years}, 86\% \text{women}) \) or NCS \( (n = 36, 41 \pm 2 \text{years old}, 78\% \text{women}) \) underwent measurements of plasma levels of catecholamines and forearm hemodynamics. Comparison data were obtained from 32 age- and gender-matched normal volunteers \( (39 \pm 2 \text{years old}, 81\% \text{women}) \). The POTS group had a relatively fast mean heart rate \( (79 \pm 2 \text{bpm}) \) during supine rest compared with the NCS group \( (69 \pm 1.6 \text{bpm}, P = 0.03) \) and normal volunteers \( (66 \pm 3 \text{bpm}, P = 0.0004) \). The POTS group also had higher mean arterial norepinephrine \( (1.61 \pm 0.11 \text{nmol/L}, n = 37) \) and epinephrine \( (0.39 \pm 0.03 \text{nmol/L}, n = 37) \) concentrations than the NCS group \( (1.03 \pm 0.12 \text{nmol/L}, n = 20, P = 0.0012; 0.21 \pm 0.03 \text{nmol/L}, n = 20, P = 0.0005) \) and normal volunteers \( (1.13 \pm 0.11 \text{nmol/L}, n = 20, P = 0.006; 0.17 \pm 0.03 \text{nmol/L}, n = 15, P = 0.0001) \). The NCS group had higher mean forearm vascular resistance \( (52 \pm 6 \text{U}) \) than the POTS group \( (36 \pm 2 \text{U}, P = 0.003) \).

Conclusions—Overall, POTS features increased heart rate and sympathetic nervous and adrenomedullary hormonal system outflows during supine rest. Increased sympathetic outflow may contribute to the relative tachycardia in POTS. NCS features forearm vasoconstriction during supine rest but not sympathoneural or adrenomedullary activation.

Key Words: syncope - nervous system, sympathetic - tachycardia - norepinephrine - epinephrine

In chronic orthostatic intolerance (COI), prolonged standing produces lightheadedness, dizziness, faintness, or syncope. Deficient sympathetic neurocirculatory regulation explains COI in autonomic failure; however, most patients with persistent orthostatic intolerance do not have sympathetic nervous system failure. After evaluation has excluded identifiable causes such as arrhythmias, seizures, and adrenal insufficiency, the pathophysiological mechanism of COI usually remains obscure. Clinicians might think the patients have mainly psychiatric disorders.

In this report, we use the term "postural tachycardia syndrome” or “POTS” for COI with excessive orthostatic tachycardia and symptoms suggestive of catecholamine effects. Patients with repeated neurocardiogenic syncope (NCS) can also have COI between episodes, without orthostatic tachycardia.1 The frequency of actual syncope depends on the individual patient’s recognition of warning symptoms and avoidance of precipitating factors. Presyncope is a sensation of near-fainting that the patient notes reliably precedes syncope, absent countermeasures such as lying down. We refer to neurocardiogenic syncope or presyncope collectively as NCS.

The present study focused on whether patients with COI and POTS or NCS have detectable neurocirculatory abnormalities during supine rest, and, if so, whether those abnormalities relate to altered functions of peripheral catecholamine systems. We asked the following questions: (1) Do groups of patients with COI and POTS or NCS differ in heart rate, blood pressure, or forearm vascular resistance during supine rest? (2) Do they differ in functions of peripheral catecholamine systems during supine rest, as indicated by antecubital venous or arterial plasma levels of norepinephrine, epinephrine, or the neuronal norepinephrine metabolite dihydroxyphenylglycol, or as indicated by the rate of entry of norepinephrine into the arterial plasma (total body norepinephrine spillover)? (3) In COI, do the hemodynamic findings correlate with the neurochemical findings during supine rest? (4) Do the results support extracardiac sympathetic denervation2 or inhibition of the cell membrane norepinephrine transporter3 as prevalent mechanisms of COI? Here, we report results of retrospective analyses of data from sizable groups of consecutively evaluated patients with COI and POTS or NCS.


TABLE 1. Hemodynamic Values in POTS, NCS, and Normal Volunteers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>POTS</th>
<th>NCS</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate supine, bpm</td>
<td>79±1.6 (86)</td>
<td>69±1.6 (35)</td>
<td>66±3 (15)</td>
</tr>
<tr>
<td>MAP supine, mm Hg</td>
<td>94±2 (86)</td>
<td>92±2 (35)</td>
<td>87±2 (17)</td>
</tr>
<tr>
<td>FBF supine, mL · min⁻¹ · dL⁻¹</td>
<td>3.6±0.3 (75)</td>
<td>3.0±0.5 (27)</td>
<td>2.6±0.3 (17)</td>
</tr>
<tr>
<td>FVR supine, U</td>
<td>36±2 (74)</td>
<td>52±6 (26)</td>
<td>39±6 (12)</td>
</tr>
<tr>
<td>Baroreflex-cardiac gain, ms/mm Hg</td>
<td>5.5±0.6 (69)</td>
<td>5.5±0.7 (26)</td>
<td>...</td>
</tr>
<tr>
<td>Dec. BPs phase II, mm Hg</td>
<td>41±2 (70)</td>
<td>42±5 (26)</td>
<td>...</td>
</tr>
</tbody>
</table>

MAP indicates mean arterial pressure; FBF, forearm blood flow; FVR, forearm vascular resistance; and Dec. BPs, decrease in systolic blood pressure.

Numbers in parentheses indicate number of subjects.

*Significant difference between POTS and NCS, P<0.05.
†Significant difference between POTS and NCS, P<0.001.

Methods

Subjects

Data were reviewed from a total of 90 consecutive POTS patients (mean age 40 years, age range 17 to 60 years, 86% women) and 36 consecutive NCS patients (mean age 41 years, age range 16 to 82 years, 78% women) who had been referred for autonomic function testing to evaluate COI under one or more National Institutes of Health clinical research protocols or in clinical consultations. The Intramural Research Board of the National Institute of Neurological Disorders and Stroke approved the study protocols. Patients gave informed written consent before participating. Data were also reviewed for an age- and gender-matched normal control group (n=32, mean age 39 years, 81% women).

All patients with NCS or POTS had COI (dizziness, lightheadedness, syncope, or presyncope during standing) that was manifest at the time of evaluation or a previously documented positive tilt-table test (excessive orthostatic tachycardia, neurally mediated hypotension, or neurally mediated syncope). None had orthostatic hypotension, defined by a consistent, persistent fall in systolic blood pressure of 20 mm Hg or more after 5 minutes of standing up, and none had baroreflex-synapathneural failure, detected by abnormal responses of beat-to-beat blood pressure during the Valsalva maneuver.

We classified patients as having POTS on the basis of an orthostatic increment of heart rate of at least 30 bpm or absolute heart rate of at least 110 bpm during orthostasis, with or without syncope or presyncope. We classified patients as having NCS by a history of chronic, repeated episodes of fainting or near-fainting, with documented tilt-evoked neurally mediated hypotension or syncope, without orthostatic tachycardia. All NCS patients in the present study had COI between episodes. Data were excluded from patients referred for COI who did not satisfy the above criteria for POTS or NCS.

Previous studies have noted an association between dysautonomia and joint hypermobility and COI. In the present study, we defined joint hypermobility liberally, by an ability to hyperextend the fingers, elbows, and knees; place an ankle behind the head; a history of repeated joint dislocation or subluxation; or an outside diagnosis of Ehlers-Danlos syndrome (n=3).

Patients could continue treatment with a serotonin reuptake blocker or fludrocortisone but tapered and stopped the use of adrenoceptor-active drugs and any tricyclic antidepressants before admission.

Testing

All testing was done in a patient observation room or the PET Department in the National Institutes of Health Clinical Center. For arterial blood sampling, a brachial catheter was placed percutaneously after local anesthesia of the overlying skin. Arm venous blood was drawn through an indwelling intravenous catheter. Samples were drawn after at least 15 minutes with the subjects supine.

Forearm blood flow was measured by venous occlusion strain gauge plethysmography (Hokanson). The circulation of the hand was not excluded, both because COI patients often complain of altered skin color of distal extremities and to prevent catecholamine responses to local ischemia. Forearm vascular resistance was calculated from the ratio of mean arterial pressure to forearm blood flow. Blood pressure was monitored continuously, either via the arterial catheter or noninvasively with a finger oscillogmometer (Finapres or Portapres, TNO) or radial tonometric (Colin) device.

For the Valsalva maneuver, each subject, while supine with head on pillow, blew into a tube connected to a sphygmonanometer, exerting 30 mm Hg of pressure for 12 seconds. Recordings from a parallel pressure transducer and direct visual inspection by an investigator confirmed adequate performance of the maneuver in all cases. The pattern of beat-to-beat blood pressure excluded sympathetic neurocirculatory failure in all subjects. For estimation of the rate of entry of endogenous norepinephrine into arterial plasma (total body norepinephrine spillover), H-norepinephrine was infused intravenously, and total body norepinephrine spillover was calculated from the specific activity of H-norepinephrine in arterial plasma.

Orthostasis consisted of standing upright or else upright tilting via a motorized tilt table for 5 minutes after the subject had been supine for at least 15 minutes. Plasma levels of catechols were assayed in our laboratory by alumina adsorption followed by liquid chromatography with electrochemical detection.

Group differences in hemodynamic and neurochemical values were assessed by ANOVA (with post hoc Fisher protected least significant difference test) and correlation coefficient calculations as appropriate (StatView 5.01, SAS Institute). Mean values were expressed ±SEM.

Results

Hemodynamics During Supine Rest

Heart rate during supine rest varied with subject group (F=11.1, P<0.0001). The POTS group had a higher mean heart rate than did the NCS group (P=0.0003) and the group of normal volunteers (P=0.0003; Table 1). The NCS and normal control groups did not differ in mean heart rate (P=0.36). In contrast with heart rate, mean arterial pressure during supine rest only tended to vary with subject group (F=2.4, P=0.10).

Forearm blood flow during supine rest did not vary with subject group (F=0.95), but forearm vascular resistance did (F=4.7, P=0.01). The NCS group had higher forearm vascular resistance than did the POTS group (P=0.003), but it was not higher than in the normal control group (P=0.67; Table 1). The POTS group and normal control group did not differ in mean forearm vascular resistance.

Plasma Catechols During Supine Rest

Arm venous plasma norepinephrine varied with subject group (F=4.5, P=0.01). The POTS group had higher arm venous norepinephrine levels than did the NCS group (P=0.03) and the group of normal volunteers (P=0.003; Table 2). The NCS group and normal control group did not differ in arm venous norepinephrine levels.
plasma norepinephrine than did the NCS group (P = 0.02) and the group of normal volunteers (P = 0.02; Table 2), whereas the NCS and normal volunteer groups did not differ (P = 0.62).

Arterial plasma norepinephrine varied with subject group (F = 7.2, P = 0.0014). The POTS group had higher arterial plasma norepinephrine than did the NCS group (P = 0.0012) and the group of normal volunteers (P = 0.006), whereas the NCS and normal volunteer groups did not differ (P = 0.63).

Total body norepinephrine spillover varied with subject group (F = 5.2, P = 0.008). The POTS group had a higher mean value than did the NCS group (P = 0.01) and the group of normal volunteers (P = 0.008); the NCS and normal volunteer groups did not differ (P = 0.77).

Arm venous plasma epinephrine did not vary significantly with subject group (F = 1.9, P = 0.15), but arterial epinephrine did (F = 11.5, P < 0.0001). The POTS group had higher arterial epinephrine than did the NCS group (P = 0.0005) and the group of normal volunteers (P = 0.0001; Table 2), whereas the NCS and normal volunteer groups did not differ (P = 0.49).

Arm venous dihydroxyphenylglycol only tended to vary with subject group (F = 2.8, P = 0.07), whereas arterial plasma dihydroxyphenylglycol varied significantly with subject group (F = 4.3, P = 0.02). The POTS group had higher arterial plasma dihydroxyphenylglycol than did the NCS group (P = 0.01) and the group of normal volunteers (P = 0.03; Table 2), whereas the NCS and normal volunteer groups did not differ (P = 0.86).

During 3H-norepinephrine infusion, the arterial plasma concentration of 3H-dihydroxyphenylglycol, normalized for the concentration of 3H-norepinephrine, varied with the subject group (F = 9.1, P = 0.0004). The POTS group had a higher mean value for normalized arterial 3H-dihydroxyphenylglycol than did the NCS group (P = 0.0002) and the normal control group (P = 0.01), whereas the NCS and normal control groups did not differ (P = 0.62; Table 2).

**Hemodynamic-Neurochemical Relationships During Supine Rest**

Across all subjects, heart rate tended to correlate with arm venous norepinephrine (r = 0.16, P = 0.07, n = 134) but correlated significantly with arterial norepinephrine (r = 0.38, P = 0.0015, n = 66) and with total body norepinephrine spillover (r = 0.28, P = 0.03, n = 59). Among COI patients, heart rate correlated with arterial and total body norepinephrine spillover (r = 0.38, P = 0.005, n = 52, and r = 0.32, P = 0.02, n = 52, respectively).

Mean arterial pressure was correlated with arm venous and arterial norepinephrine (r = 0.24, P = 0.0006, n = 136; r = 0.33, P = 0.0006, n = 104) and with total body norepinephrine spillover (r = 0.30, P = 0.01, n = 68) across all subjects. Among COI patients, mean arterial pressure correlated with arterial and total body norepinephrine spillover (r = 0.38, P = 0.005, n = 52, and r = 0.35, P = 0.02, n = 46, respectively).

Forearm vascular resistance tended to correlate positively with arm venous norepinephrine (r = 0.17, P = 0.07, n = 111) but not with arterial norepinephrine (r = 0.15, P = 0.27, n = 59) or with total body norepinephrine spillover (r = 0.17, P = 0.20, n = 56). Among COI patients, forearm vascular resistance did not correlate with arm venous norepinephrine (r = 0.19, P = 0.21, n = 47), arterial norepinephrine (r = 0.19, P = 0.21, n = 47), or total body norepinephrine spillover (r = 0.22, P = 0.14, n = 44).

Heart rate correlated positively with arm venous epinephrine across all subjects (r = 0.21, P = 0.01, n = 132) and in patients with COI (r = 0.21, P = 0.02, n = 118). Heart rate tended to correlate positively with arterial epinephrine across all subjects (r = 0.20, P = 0.12, n = 61) but not in patients with COI (r = 0.14, P = 0.32, n = 52).

Forearm vascular resistance correlated negatively with arm venous epinephrine across all subjects (r = 0.27, P = 0.0005, n = 110) and in patients with COI (r = 0.27, P = 0.007, n = 98). Forearm vascular resistance did not correlate significantly with arterial epinephrine, either across all subjects (r = 0.19, P = 0.15, n = 56) or in patients with COI (r = 0.22, P = 0.13, n = 47).

Mean arterial pressure did not correlate with arm venous epinephrine (r = 0.08, P = 0.34, n = 134) but did tend to correlate with arterial epinephrine (r = 0.22, P = 0.08, n = 63). Among COI patients, mean arterial pressure did not correlate with arterial epinephrine (r = 0.18, P = 0.21, n = 52).

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**TABLE 2. Neurochemical Values in POTS, NCS, and Normal Volunteers**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>POTS</th>
<th>NCS</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm venous NE, nmol/L</td>
<td>1.93±0.10 (88)*</td>
<td>1.49±0.17 (35)</td>
<td>1.36±0.13 (18)</td>
</tr>
<tr>
<td>Arterial NE, nmol/L</td>
<td>1.61±0.11 (37)*</td>
<td>1.03±0.12 (20)</td>
<td>1.13±0.10 (20)</td>
</tr>
<tr>
<td>Total body NE SO, nmol/min</td>
<td>3.97±0.38 (30)*</td>
<td>2.59±0.42 (19)</td>
<td>2.41±0.31 (16)</td>
</tr>
<tr>
<td>Arm venous EPI, nmol/L</td>
<td>0.12±0.01 (87)</td>
<td>0.09±0.01 (35)</td>
<td>0.09±0.02 (17)</td>
</tr>
<tr>
<td>Arterial EPI, nmol/L</td>
<td>0.39±0.03 (37)†</td>
<td>0.21±0.03 (20)</td>
<td>0.17±0.03 (15)</td>
</tr>
<tr>
<td>Arm venous DHPG, nmol/L</td>
<td>5.76±0.25 (81)*</td>
<td>4.68±0.30 (35)</td>
<td>5.22±0.37 (17)</td>
</tr>
<tr>
<td>Arterial DHPG, nmol</td>
<td>5.06±0.22 (38)*</td>
<td>4.14±0.21 (20)</td>
<td>4.21±0.38 (17)</td>
</tr>
<tr>
<td>3H-DHPG/3H-NE, nmol</td>
<td>0.09±0.01 (28)†</td>
<td>0.05±0.00 (20)</td>
<td>0.05±0.01 (10)</td>
</tr>
</tbody>
</table>

NE indicates norepinephrine; SO, spillover; DHPG, dihydroxyphenylglycol; and 3H, tritium-labeled. Numbers in parentheses indicate number of subjects.

*Significant difference between POTS and NCS, P < 0.05.
†Significant difference between POTS and NCS, P < 0.001.
TABLE 3. Hemodynamic and Neurochemical Responses to Orthostasis in POTS and NCS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>POTS</th>
<th>NCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate upright, bpm</td>
<td>106±3 (64)‡</td>
<td>78±2 (17)</td>
</tr>
<tr>
<td>Δ Heart rate upright, bpm</td>
<td>31±2 (64)‡</td>
<td>12±2 (17)</td>
</tr>
<tr>
<td>SBP upright, mm Hg</td>
<td>132±3 (47)</td>
<td>129±6 (12)</td>
</tr>
<tr>
<td>DBP upright, mm Hg</td>
<td>78±2 (47)</td>
<td>71±4 (12)</td>
</tr>
<tr>
<td>MAP upright, mm Hg</td>
<td>93±3 (59)</td>
<td>90±4 (16)</td>
</tr>
<tr>
<td>FVR upright, U</td>
<td>52±5 (51)</td>
<td>53±4 (8)</td>
</tr>
<tr>
<td>Δ FVR upright, U</td>
<td>20±5 (51)</td>
<td>6±5 (8)</td>
</tr>
<tr>
<td>NE upright, nmol/L</td>
<td>3.86±0.21 (65)*</td>
<td>2.82±0.30 (18)</td>
</tr>
<tr>
<td>Δ NE upright, nmol/L</td>
<td>2.00±0.17 (65)†</td>
<td>1.16±0.19 (18)</td>
</tr>
<tr>
<td>FxΔ NE upright</td>
<td>1.25±0.10 (65)</td>
<td>0.88±0.14 (18)</td>
</tr>
<tr>
<td>DHPG upright, nmol/L</td>
<td>6.28±0.28 (59)</td>
<td>5.60±0.55 (16)</td>
</tr>
<tr>
<td>Δ DHPG upright, nmol/L</td>
<td>0.78±0.12 (59)</td>
<td>0.37±0.10 (16)</td>
</tr>
<tr>
<td>FxΔ DHPG upright</td>
<td>0.15±0.02 (59)</td>
<td>0.39±0.18 (17)</td>
</tr>
<tr>
<td>Δ DHPG/Δ NE</td>
<td>0.52±0.06 (51)</td>
<td>0.34±0.12 (14)</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; FVR, forearm vascular resistance; NE, norepinephrine; FxΔ, fractional change; and DHPG, dihydroxyphenylglycol.

Numbers in parentheses indicate numbers of subjects.

*Significant difference between POTS and NCS, P<0.05.
†Significant difference between POTS and NCS, P<0.01.
‡Significant difference between POTS and NCS, P<0.001.

Orthostasis

In response to standing or upright tilting for 5 minutes, the POTS group had increased forearm vascular resistance (dependent-means t=3.7, P=0.0005), whereas the NCS group did not (Table 3); however, repeated-measures ANOVA did not show that the patient groups differed in the forearm vascular resistance increment during orthostasis (F=1.4, P=0.23, n=58). As expected, the 2 patient groups differed in the mean increment in heart rate during orthostasis, as judged by the group–heart rate increment interaction effect in the repeated-measures ANOVA (F=22.7, P<0.0001; Table 3).

After 5 minutes of orthostasis, the increment in arm venous norepinephrine in the POTS group exceeded that in the NCS group, as judged by the group-norepinephrine increment interaction effect in the repeated-measures ANOVA (F=6.4, P=0.01; n=83). The POTS group had a higher mean norepinephrine concentration during orthostasis (F=6.0, P=0.02, n=83) and tended to have a larger proportionate increment in arm venous norepinephrine (F=3.0, P=0.09, n=83) than did the NCS group (Table 3).

Among COI patients, the increment in heart rate during orthostasis correlated positively with the increment in arm venous norepinephrine (r=0.30, P=0.01, n=76). The increment in arm venous dihydroxyphenylglycol during orthostasis also correlated positively with that in arm venous norepinephrine (r=0.42, P=0.0002). The POTS group tended to have a larger increment in dihydroxyphenylglycol than did the NCS group (F=2.9, P=0.10, n=74; Table 3). The mean ratio of the increments in norepinephrine and dihydroxyphenylglycol did not differ between the 2 groups (F=1.9, P=0.18, n=64). The POTS and NCS groups also did not differ in terms of the absolute increment in arm venous dihydroxyphenylglycol during orthostasis, the ratio of the absolute increment in arm venous dihydroxyphenylglycol to the absolute increment in arm venous norepinephrine, the fractional increment in arm venous dihydroxyphenylglycol, or the ratio of the fractional increment in arm venous dihydroxyphenylglycol to the fractional increment in arm venous norepinephrine (Table 3).

Valsalva Maneuver

The extent of fall in systolic blood pressure during phase II of the Valsalva maneuver did not differ between the POTS and NCS groups (F=0.08, P=0.78, n=94; Table 1). Similarly, baroreflex-cardiovascular gain, calculated from the slope of the relationship between interbeat interval (with a 1-beat delay) and systolic blood pressure during phase II of the maneuver, also did not differ between the POTS and NCS groups (F=0.02, P=0.88, n=93).

Joint Hypermobility

Among COI patients, 9 had joint hypermobility, and all 9 of these had POTS. Arm venous plasma norepinephrine levels in this subgroup did not differ from those in the other POTS patients, but mean plasma norepinephrine appeared to increase excessively during standing (by 210±46%, approximately twice the normal mean).

Possible Treatment Effects

For all dependent hemodynamic and neurochemical variables, the 17 NCS patients who had been treated with a selective serotonin reuptake inhibitor (SSRI) did not differ from the 19 NCS patients who had not been treated with an SSRI, and the 44 POTS patients who had been treated with an SSRI did not differ from the 46 POTS patients who had not been treated with an SSRI. Similarly, the 13 NCS patients who had been treated with fludrocortisone did not differ from the 23 NCS patients who had not, and the 43 POTS patients who had been treated with fludrocortisone did not differ from the 47 POTS patients who had not. Too few NCS patients had not been treated with either an SSRI or fludrocortisone to conduct meaningful statistical comparisons with the corresponding POTS patients.

Discussion

In this study, patients with COI associated with POTS or NCS had neurocirculatory abnormalities that were detectable during supine rest. The pattern of abnormalities differed between the 2 groups. POTS patients had relative tachycardia and increased values for indices of sympathetic nervous and adrenomedullary hormonal system outflows, whereas NCS patients had forearm vasoconstriction and generally normal indices of sympathetic nervous and adrenomedullary hormonal system outflows. Few studies have compared POTS with NCS. Instead, researchers have equated COI with POTS and presumed that in NCS, between acute episodes of fainting or near-fainting, the patients do not have COI. In the present ongoing series, however, among more than 150
patients referred for persistent COI without autonomic failure, $\approx 60\%$ have satisfied criteria for POTS and $\approx 25\%$ have satisfied criteria for NCS without POTS.

Many previous studies have found evidence for relative tachycardia or sympathetic nervous system activation in POTS or COI. In contrast, few studies have assessed adrenomedullary hormonal system activity in POTS, and to the best of our knowledge, none has used arterial epinephrine data. In the present study, POTS patients had clear evidence of adrenomedullary activation during supine rest, based on high arterial epinephrine levels, whereas arm venous epinephrine levels actually were below normal. Because extraction of circulating catecholamines by tissues of the forearm varies inversely with local blood flow, arm venous epinephrine can substantially underestimate arterial epinephrine in the setting of forearm vasoconstriction.

Normally, the heart contributes only $\approx 3\%$ to the rate of entry of norepinephrine into arterial plasma. Therefore, accounting for the elevated arterial plasma norepinephrine and epinephrine levels and high rates of total body norepinephrine spillover in POTS would appear to require that POTS entail not only cardiac sympathetic activation, as reported by our group previously, but also extracardiac sympathetic activation. This inference in turn has meaning for current hypotheses about pathophysiological mechanisms of POTS, as follows.

Decreased clearance of circulating catecholamines via the cell membrane norepinephrine transporter could potentially explain high plasma catecholamine concentrations in POTS. Affected members of a family with POTS carry a hypofunctional mutation of the cell membrane norepinephrine transporter, and in healthy people, administration of any of several drugs that inhibit the transporter can elicit orthostatic intolerance and tachycardia. The finding of high total body norepinephrine spillover in the POTS group indicates that in POTS, high circulating norepinephrine levels do not result from decreased removal from the circulation but from increased release into it.

Although neuronal uptake via the cell membrane norepinephrine transporter plays a major role in inactivation of norepinephrine released from cardiac sympathetic nerves, neuronal uptake plays only a minor role in clearance of catecholamines from the plasma. Therefore, the finding of normal clearance of norepinephrine from arterial plasma would not necessarily exclude decreased activity of the membrane transporter in POTS. Given the sources and meanings of plasma levels of dihydroxyphenylglycol, however, the present findings of normal arterial plasma $^{3}H$-dihydroxyphenylglycol concentrations, adjusted for $^{3}H$-norepinephrine concentrations, and normal increments in plasma dihydroxyphenylglycol for given increments in plasma norepinephrine during orthostasis in POTS patients cast doubt on the notion of norepinephrine transporter inhibition as a prevalent pathophysiological mechanism of POTS.

According to another concept, POTS results from sympathetic denervation in extracardiac organs, with compensatory activation of cardiac sympathetic outflow. Because cardiac norepinephrine spillover contributes so little to norepinephrine levels in the arterial circulation, the notion of extracardiac sympathetic denervation would predict that POTS patients should have normal or decreased arterial norepinephrine levels at baseline and normal or attenuated increments in plasma norepinephrine during orthostasis. Instead, the POTS group had high plasma norepinephrine levels during supine rest and augmented increments in plasma norepinephrine during orthostasis compared with values in NCS patients and normal control subjects.

The liver efficiently removes and metabolizes the circulating catecholamines that reach it via the portal vein. Arterial norepinephrine concentrations, therefore, do not reflect release of the neurotransmitter from splanchnic sympathetic nerves. The present results do not exclude the possibility of splanchnic sympathetic denervation and secondary increases in sympathetic traffic to other organs. A recent report provided support for increased splanchnic-mesenteric capacitance in POTS. Whether patients with POTS have decreased splanchnic norepinephrine spillover remains unknown.

We hypothesize that overall in POTS, increased sympathetic nervous and adrenomedullary hormonal system outflows reflect compensatory activation in response to decreased venous return to the heart. Several processes decrease venous return, including blood or extracellular fluid volume depletion, venous pooling (from increased venous compliance or increased delivery of blood to veins as a result of limited arteriolar vasoconstriction), extravasation, or splanchnic sympathetic denervation. Moreover, these possibilities are not mutually exclusive. Excessive orthostatic blood pooling would not explain the multiple hemodynamic and neurochemical abnormalities in POTS when the patients were supine.

Patients with NCS have been reported to have normal plasma levels of norepinephrine, rates of peroneal sympathetic nerve traffic, power spectra of heart rate variability, and forearm vascular resistance during supine rest. In the present study, NCS patients had high forearm vascular resistance compared with POTS patients. The NCS patients in the present study may have differed from those in other studies because patients in the present study all had COI between episodes, as well as other nonspecific symptoms. Moreover, because of well-known substantial individual differences in both POTS and NCS, it may be necessary to test large groups of patients, such as was done in the present study, in order for statistically significant group differences to emerge.

NCS has been reported to be associated with attenuated sympathetic nervous responses to orthostatic stimuli, as evidenced by a tendency to inhibition of directly recorded skeletal sympathetic outflow during upright tilting, and healthy volunteers predisposed to NCS have decreased forearm norepinephrine spillover during exposure to non-hypotensive lower-body negative pressure. This attenuation can help explain relatively small increments in forearm vascular resistance during orthostasis or lower-
body negative pressure in NCS patients, as noted previously and confirmed in the present study.

In NCS, increased vascular resistance despite normal delivery of norepinephrine to adrenoceptors might reflect structural adaptations in blood vessel walls, renin-angiotensin-aldosterone system activation, \( \alpha \)-adrenoceptor upregulation, or decreased local production of vascular relaxing factors. An episodic, centrally evoked neuroendocrine pattern, characterized by widespread sympathetic nervous inhibition and adrenomedullary hormonal activation, might further attenuate reflexive cardiovascular responses to decreased venous return to the heart and initiate a neurocirculatory positive feedback loop that would lead to a critical decline in brainstem blood flow and loss of consciousness.

**Study Limitations**

The present study had the limitations inherent in a retrospective study. In particular, because our approach was essentially observational, rather than hypothesis driven, the obtained correlations between hemodynamic and neurochemical results may not have indicated cause-and-effect relationships. Because we allowed subjects to continue treatment with an SSRI or fludrocortisone, we could not exclude the possibility of effects of these drugs on the results; however, comparisons of treated and untreated subgroups of POTS and NCS patients did not yield evidence of any treatment effects for any of the dependent hemodynamic or neurochemical variables. There were relatively small data sets for NCS patients and normal control subjects during orthostasis. All the patients in this study had COI, as well as other nonspecific symptoms between episodes, and so the findings in the NCS group might not apply to the population of NCS patients who do not have COI.

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