Cerebral autoregulation is preserved in postural tachycardia syndrome

Ronald Schondorf, Julie Benoit, and Reuben Stein
Autonomic Reflex Laboratory, Department of Neurology, McGill University,
Sir Mortimer B. Davis Jewish General Hospital, Montreal, Quebec, Canada

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Schondorf, Ronald, Julie Benoit, and Reuben Stein. Cerebral autoregulation is preserved in postural tachycardia syndrome. J Appl Physiol 99: 828–835, 2005. First published April 28, 2005; doi:10.1152/japplphysiol.00225.2005.—To test whether cerebral autoregulation is impaired in patients with postural tachycardia syndrome (POTS), we evaluated 17 healthy control subjects and 27 patients with POTS. Blood pressure, heart rate, and cerebral blood velocity (transcranial Doppler) were recorded at rest and during 80° head-up tilt (HUT). Static cerebral autoregulation, as assessed from the change in cerebrovascular resistance during HUT, was the same in POTS and in controls. The properties of dynamic cerebral autoregulation were inferred from transfer gain, coherence, and phase of the relationship between blood pressure and cerebral blood velocity estimated from filtered data segments (0.02–0.8 Hz). Dynamic cerebral autoregulation of patients with POTS did not differ from that of controls. The patients’ dynamic cerebral autoregulation did not change over the course of HUT, despite increased tachycardia suggestive of worsening orthostatic stress. Inflation of military anti-shock trouser pants substantially reduced the tachycardia of patients with POTS without affecting cerebral autoregulation. Symptoms of orthostatic intolerance were reduced in one-half of the patients following military anti-shock trouser pants inflation. We conclude that cerebral perfusion and autoregulation in many patients with POTS do not differ from that of normal control subjects.

Regardless of pathophysiology, all patients with POTS are significantly disabled by the constellation of symptoms noted above (2).

Lightheadedness and impaired concentration while upright or following other orthostatic stressors are among the most disabling symptoms experienced by patients with POTS. It has generally been assumed that these symptoms are due to cerebral hypoperfusion, despite maintenance of normal blood pressure (BP) (29). The changes in cerebral perfusion during standing in patients with POTS have been measured using transcranial Doppler sonography of the middle cerebral artery (MCA). Some investigators did find that MCA cerebral blood velocity (CBV) decreased excessively during orthostatic stress (23, 34), whereas others found no such change in CBV, despite the presence of symptoms suggestive of cerebral hypoperfusion (22, 38). The reduction in CBV during orthostatic stress has been attributed to excessive hyperventilation (34) or to exaggerated sympathetic activity directed to cerebral vasculature (28).

Cerebral autoregulation is defined as the intrinsic capacity of cerebral vasculature to maintain cerebral blood flow constant over a wide range of cerebral perfusion pressures (35, 37). Cerebral autoregulation has been modeled as both a static and a dynamic process (35, 42, 44), with the latter being a somewhat more sensitive index of a threatened cerebral circulation (9). Reduced cerebral perfusion during orthostatic stress will occur if cerebral autoregulation is overwhelmed or impaired (12). Normal individuals subjected to high levels of orthostatic stress simulated by lower body negative pressure (LBNP) have reduced cerebral perfusion and impaired dynamic cerebral autoregulation (4, 54). Cerebral perfusion is significantly reduced by LBNP in normal individuals made orthostatically intolerant by prolonged head-down bed rest (55). Severe hemorrhagic hypotension in primates also causes cerebral vasosconstriction (15). We hypothesized that patients with POTS who experience greater levels of orthostatic stress during standing than do unaffected individuals will have reduced cerebral perfusion due to impairment of cerebral autoregulation.

METHODS

We evaluated 27 patients (2 men, 25 women) with POTS as defined above. Although all had symptomatic orthostatic intolerance, none had recurrent episodes of syncope. In all patients, history, physical examination, routine clinical chemistry, complete blood count, and other relevant examinations (Holter monitor, electroencephalogram, electrocardiogram, and echocardiogram) did not reveal the cause of POTS. Patients participating in this study did not take medication of any kind. Seventeen healthy subjects (6 men and 11 women) with no history of orthostatic intolerance served as the control group. Both

Address for reprint requests and other correspondence: R. Schondorf, Dept. of Neurology, Sir Mortimer B. Davis Jewish General Hospital, 3755 chemin de la Côte St. Catherine, Montreal Quebec, Canada H3T 1E2 (E-mail: ronald.schondorf@mcgill.ca).
The continuous waveforms of BP, CBV, and respiration were band-pass filtered between 0.02 and 0.8 Hz. Filtered data segments of 4,096 points (204.8 s) were subsampled at 2.5 Hz. Periodograms were constructed from Hanning-windowed segments of 256 points overlapped by 50%. The power of the low-frequency BP and CBV bands was integrated by using the commonly accepted bandwidth definition of 0.04–0.15 Hz (7, 8, 44). In addition, the power in the frequency band of 0.02–0.12 Hz was integrated for comparison, as this was the frequency band at which the average dynamic gain and phase were analyzed (see below). Transfer functions were constructed from Hanning-windowed segments of 128 points overlapped by 69%. For each transfer function, squared coherence, phase delay, and transfer gain were calculated. The phase delay is defined as positive when CBV leads BP. Transfer gain expresses the degree to which oscillations in input (BP) are transmitted to output (CBV). Dividing transfer gain by mean conductance of the analyzed data segment normalizes the gain.

Normalized gain of <1 indicates attenuation of the transmitted BP fluctuations to CBV, i.e., dynamic autoregulation. Minimal dynamic gain was calculated as the average of points between 0.02 and 0.04 Hz, the frequency range at which the best attenuation of transmitted BP fluctuations was observed. To facilitate comparison of curves of gain and phase between control and POTS subjects, we averaged the points between 0.02 and 0.12 Hz, where the normalized gain was <1. 3 × 2 ANOVAs with repeated measures were used for comparisons of baseline and HUT between control and POTS subjects for the cardiovascular and cerebrovascular data. Two HUT periods were sampled: the first beginning ~1 min after the start of tilt (early HUT), and a second period beginning ~4 min before the end of HUT (late HUT). The late HUT period used for construction of periodograms and transfer functions began ~3 min before the end of the HUT. For comparison of periodograms or of transfer function analyses between control and POTS groups, a 2 × 2 ANOVA with repeated measures was used. If significant differences were found (P < 0.05), Dunnett’s procedure for multiple comparisons was used to assess differences between the various groups. For comparisons between groups of patients with greatly different sample sizes, the Mann-Whitney nonparametric U-test was used. For other comparisons between control and POTS groups, such as age, height, weight, etc., Student’s t-tests were used. Data are expressed as means ± SE.

RESULTS

Cardiovascular and cerebrovascular profiles during HUT. Representative beat-to-beat profiles of HR, systolic and diastolic BP, systolic and diastolic CBV, and calculated CVR from a control subject and a POTS patient during HUT are shown in Fig. 1. The complete profiles of the averaged data during early and late HUT from the 17 controls and 27 patients with POTS are shown in Fig. 2, and the averaged raw values from these three periods are provided in Table 1. Supine HR, systolic and diastolic BP, and systolic and diastolic CBV were all significantly increased in POTS patients relative to control subjects. The averaged absolute changes in the cardiovascular responses from baseline were compared during early and late HUT (all data in this section expressed as POTS vs. controls). It should be noted that patients with POTS were tilted for a shorter duration than were control subjects (16.9 ± 2.1 vs. 36.9 ± 2.0 min, P < 0.0001). The responses to late HUT should, therefore, be considered as being the response to the maximum orthostatic stress imposed by our experimental protocol. POTS patients had greater increases in HR, during both early (36.5 ± 2.5 vs. 17.5 ± 2.4 beats/min, P < 0.0001) and late HUT (48.7 ± 1.8 vs. 29.6 ± 2.1 beats/min, P < 0.0001) and decreased systolic BP during early (<5.0 ± 2.0 vs. 5.3 ± 4.0 mmHg, P = 0.03) and late (<11.7 ± 2.3 vs. 6.4 ± 4.2 mmHg, P = 0.001) HUT. The increase in diastolic BP during early HUT was similar (9.0 ± 1.8 vs. 7.2 ± 1.4 mmHg, P = 0.5) in both groups but, during late HUT, was less in POTS (10.0 ± 1.9 vs. 15.9 ± 2.0 mmHg, P = 0.02).

In contrast to the cardiovascular profile, the percent decreases in systolic (early HUT: 84.9 ± 2.6 vs. 89.4 ± 2.0% of baseline, P = 0.2; late HUT: 78.8 ± 2.1 vs. 77.9 ± 2.5% of baseline, P = 0.8) and diastolic (early HUT: 88.0 ± 3.0 vs. 90.7 ± 2.6% of baseline, P = 0.5; late HUT: 80.0 ± 2.1 vs. 78.2 ± 3.7% of baseline, P = 0.7) CBV were not different. The percent decrease in CVR during early HUT, an index of static cerebral autoregulation, was also similar (85.6 ± 3.3 vs. 89.0 ± 4.5%, P = 0.7), whereas the percent decrease in CVR during late HUT was less in POTS than in normal controls.
In nine POTS subjects, end-tidal CO$_2$ was measured. CO$_2$ decreased from $4.57 \pm 0.16$ to $3.86 \pm 0.14\%$ during early HUT ($P = 0.0002$) and to $3.62 \pm 0.15\%$ by late HUT (no difference between early and late HUT, $P = 0.3$). Respiratory frequency of patients with POTS was similar to that of normal control subjects (see spectra in Fig. 4F).

In eight POTS patients, inflating MAST pants after $\sim 5$ min of HUT reduced the orthostatic stress of HUT. The profiles of the averaged data from the eight patients are shown in Fig. 3, and averaged raw values are provided in Table 2. MAST pants inflation significantly decreased HR and increased SV and systolic CBV. Mean CBV increased from $49.1 \pm 4.2$ to $53.8 \pm 3.6$ cm/s ($P = 0.01$), which represented an increase from $82.5 \pm 3.3\%$ of the baseline level before MAST pants inflation to $91.1 \pm 3.3\%$ of the pretilt level during the MAST pants inflation. End-tidal CO$_2$ (measured in only 4 patients) decreased significantly during tilt before inflation of MAST pants ($4.66 \pm 0.29$ to $3.91 \pm 0.15\%$, $P = 0.04$) and recovered during MAST pants inflation ($4.20 \pm 0.17\%$, $P = 0.01$ compared with HUT alone). Deflation of the MAST pants was associated with an increase in HR, a decrease in SV, and a decrease in CBV (Fig. 3). Despite the obvious effect of MAST pants inflation, only four patients noted substantial symptomatic improvement during this maneuver.

Fluctuations in BP and CBV in controls and in POTS subjects during HUT. Both control subjects and POTS patients exhibited similar spontaneous low frequency (<0.1 Hz) oscillations in BP and CBV, although the magnitudes of both the BP and CBV oscillations were significantly greater in patients with POTS (Fig. 4, D and E; Table 3). The increased magnitude of these low-frequency fluctuations was due to greater response to orthostatic stress. Reduction of orthostatic stress by MAST pants inflation decreased BP power from $315.8 \pm 56.4$
to 134.2 ± 22.9 mmHg²/Hz (P = 0.005) and CBV power from 209.1 ± 22.2 to 86.7 ± 18.7 (cm/s)²/Hz (P = 0.0004). The power of the fluctuations during MAST pants inflation did not significantly differ from that of the normal control BP and CBV oscillations during HUT (P = 0.4 for BP and P = 0.7 for CBV).

Dynamic cerebral autoregulation during HUT. The transfer function signatures of controls and POTS subjects shown in Fig. 4, A–C, were essentially superimposable. Coherence between BP and CBV remained >0.5 in the frequency range between 0.06 ± 0.01 and 0.36 ± 0.03 Hz in control subjects and 0.05 ± 0.01 and 0.39 ± 0.02 Hz in patients with POTS (average coherence: 0.71 ± 0.03 for controls vs. 0.72 ± 0.02 for POTS). Phase was positive in this frequency range, revealing that the oscillations in blood flow lead those in pressure. Gain was <1 at frequencies <0.12 Hz, indicating that flow is stabilized in the presence of fluctuation in pressure at these frequencies. The values for minimal dynamic gain, average dynamic gain, and average phase, presented in Table 3, show no difference between control and POTS subjects. Reduction of orthostatic stress by inflation of MAST pants during HUT did not significantly alter the transfer function curves in the eight POTS patients tested.

Dynamic cerebral autoregulation in POTS patients remained stable over the duration of the HUT, despite the progressive increase in HR (an index of increased orthostatic stress). Figure 5 presents data taken from 22 subjects with POTS who had HUTs of sufficient duration to allow for construction of separate transfer functions from the beginning and from the end of HUT. As shown in Fig. 5, D and E, the magnitudes of the BP and CBV fluctuations were stable over the duration of the tilt. Moreover, the transfer function curves from these two times are essentially identical. This visual impression was confirmed by showing no statistical difference between the paired data of minimal and average gain, phase, and BP and CBV oscillations, taken from these 22 subjects.

Dynamic cerebral autoregulation in controls and in subjects with POTS while supine. The dynamic cerebral autoregulation of both groups was also assessed in the absence of orthostatic stress from data segments obtained during the supine pre-HUT period. As shown in Fig. 6 and in Table 3, there was no difference in the magnitude of the BP or CBV fluctuations at

Table 1. Averaged cardiovascular and cerebrovascular responses in controls and POTS

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Values are means ± SE. HUT, head-up tilt; POTS, postural tachycardia syndrome; HR, heart rate; BP, blood pressure; CBV, cerebral blood velocity; CVR, cerebrovascular resistance. *Comparison of POTS with controls during same orthostatic stress, †comparison of early HUT vs. supine, and ‡comparison of late HUT vs. early HUT: P < 0.05.
any frequency range or in the transfer function signatures of supine controls compared with those of supine subjects with POTS. In the absence of orthostatic stress, the magnitude of the BP fluctuations was less in both groups (Table 3). Both the minimal and average dynamic gains were elevated in the supine control group compared with HUT. In the POTS patients, the minimal dynamic gain was significantly greater while supine compared with HUT, but not the average dynamic gain.

**DISCUSSION**

The results of this study provide several new insights concerning cerebral autoregulation in POTS. First, contrary to our hypothesis, patients with POTS did not have impaired cerebral perfusion compared with normal control subjects, despite the presence of a cardiovascular profile during HUT, suggestive of increased orthostatic stress. In this regard, our data confirm the observations of others who did not observe reductions in CBV during orthostatic stress in POTS (22, 38) and are not consistent with other studies in which CBV was excessively reduced during HUT (23, 34).

Second, reduction of orthostatic stress with MAST pants inflation effectively reversed the HUT-induced tachycardia but only reduced symptoms of lightheadedness in one-half of the eight patients tested. Third, static autoregulation, as assessed from the CVR response to early HUT, was similar in POTS and normal control subjects. Fourth, dynamic cerebral autoregulation of patients with POTS did not differ from that of controls.

| Table 3. Comparison of power spectra and transfer function analysis: controls vs. POTS |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                  | Supine          | POTS            | HUT             | POTS            |
| **BP power, mmHg^2/Hz** |                  |                 |                 |                 |
| (0.02–0.12 Hz) | 122.8±24.7      | 145.3±25.3      | 211.0±28.9      | 322.1±35.6†     |
| (0.04–0.15 Hz) | 68.8±12.8       | 99.6±17.9       | 172.9±26.5†     | 252.5±27.5†     |
| **CBV power, (cm/s)^2/Hz** |                  |                 |                 |                 |
| (0.02–0.12 Hz) | 123.4±32.2      | 143.6±23.1      | 128.3±16.3      | 208.3±25.5†     |
| (0.04–0.15 Hz) | 58.6±10.7       | 89.0±13.9       | 96.4±14.0       | 162.0±20.8†     |
| **Gain** |                  |                 |                 |                 |
| (0.02–0.04 Hz) | 0.82±0.12       | 0.70±0.07       | 0.46±0.05†      | 0.48±0.04†      |
| (0.02–0.12 Hz) | 0.86±0.07       | 0.79±0.04       | 0.66±0.03†      | 0.70±0.04       |
| **Phase, rad** |                  |                 |                 |                 |
| (0.02–0.12 Hz) | 0.58±0.14       | 0.76±0.08       | 0.64±0.08       | 0.83±0.06       |

Values are means ± SE. Values in parentheses are bandwidths. *Comparison of POTS with controls during same orthostatic stress and †comparison of HUT vs. supine: P < 0.05.
controls. Moreover, dynamic cerebral autoregulation did not change over the course of HUT in patients with POTS, even though the cardiovascular response did.

In this study, we used transcranial Doppler to measure cerebral perfusion, because this technique is the only one currently available that permits the noninvasive, prolonged monitoring of rapid changes in cerebral perfusion needed to assess dynamic cerebral autoregulation. We have previously discussed the limitations of this technique as well as the validity of using linear transfer function analysis to assess dynamic cerebral autoregulation (42, 44). The MCA was insonated because stable, long-term recordings can be easily

Fig. 5. Group-averaged transfer function gain (A), phase (B), coherence (C), and spectral analysis of the fluctuations in BP (D), CBV (E), and respiration (F) in 22 POTS patients who had HUT of sufficient duration to allow construction of separate transfer functions at the beginning and end of HUT.

Fig. 6. Group-averaged transfer function gain (A), phase (B), coherence (C), and spectral analysis of the fluctuations in BP (D), CBV (E), and respiration (F) in supine control subjects and POTS patients.
obtained and because this artery supplies a substantial portion of cerebral blood flow to the anterior circulation. The dynamic autoregulatory response characteristics of the MCA largely mirror those of arteries of the posterior circulation (21, 36, 40).

In a study of nine patients with POTS, the α-adrenergic blocker phenotolamine, volume replacement with isotonic saline, or infusion of phentolamine all acted to reverse the significant CBV reduction during orthostatic stress (28). These data suggest that, in this subgroup of patients with POTS, cerebral hypoperfusion might be due to exaggerated sympathetically mediated cerebral vasoconstriction (8, 53). The cerebral vasculature receives a rich sympathetic innervation, but the effect of this innervation on cerebral blood flow in humans is unclear (20). Whereas numerous animal experiments have shown that sympathetic denervation does not alter resting cerebral blood flow (6), in humans, stellate ganglionic blockade increases ipsilateral cerebral blood flow (51). Similarly, sympathetic denervation does not alter cerebral autoregulation in normotensive animals (6), but pharmacological ganglionic blockade with trimethaphan appears to attenuate dynamic cerebral autoregulation in humans (53). The effect of generalized sympathoexcitation on cerebral blood flow in humans is even less well understood. Sympathoexcitation induced by immersing the hand in ice water may either increase (39) or decrease (47) CVR, whereas sympathoexcitation induced by total body surface skin cooling actually improves orthostatic tolerance and increases CBV during the orthostatic stress of incremental LBNP (11). It is also not clear that exaggerated generalized sympathoexcitation actually occurs in most patients with POTS. As reviewed in the Introduction, not all patients with POTS manifest exaggerated generalized sympathetic activity. Indeed, the same research group that postulated increased sympathetic outflow to cerebral vasculature in POTS also found that the postganglionic sympathetic response to standing was blunted in these patients relative to controls (17).

Others have shown that the exaggerated decrease in CBV in patients with POTS is due to hyperventilation, although the cause of this hyperventilation is unknown (34). It has been suggested that hyperventilation occurred as patients increased depth of respiration to increase venous return and improve orthostatic tolerance. We have not observed increased respiratory frequency in our patients, nor have we found evidence of hyperventilation in a subgroup of patients in whom CO2 was measured. Hyperventilation would also be expected to improve dynamic cerebral autoregulation in these patients (1, 13). However, this group of investigators has also documented abnormally prolonged CBV recovery during phase IV of the Valsalva maneuver, an observation that suggests that autoregulation is actually impaired in some of their patients with POTS (30).

As noted above, we did not find evidence of impaired cerebral perfusion or impaired static or dynamic autoregulation in our patients with POTS. It is unlikely that our patients represent a subpopulation that is distinctly different from that studied by others. Both the symptom and hemodynamic profiles are indistinguishable from those described by others. Moreover, many of the patients studied by at least one group (34) had evidence of mild POTS only, despite symptoms and evidence of impaired cerebral perfusion.

Our data clearly show that many with POTS who have symptoms suggestive of cerebral hypoperfusion during orthostatic stress show normal responsiveness of the anterior circulation during HUT. What then is the pathophysiology of the symptoms experienced by these patients? One possibility is that symptoms arise from impaired perfusion of structures (e.g., vestibular nuclei) receiving blood supply from the posterior circulation. As noted above, there is no evidence that the dynamic autoregulatory response characteristics of the posterior circulation differ from that of the anterior circulation (21, 36, 40). Further studies, however, are required to directly confirm this in patients with POTS. A second possibility is that cerebral oxygenation is impaired in patients with POTS. This possibility has been documented in one group of young subjects using near-infrared spectroscopy and recording from probes placed over the forehead (50). It is unlikely that impaired cerebral oxygenation accounts for these symptoms in our patients. When autoregulation fails, oxygen extraction fraction increases substantially as a final attempt to maintain cerebral oxygen metabolism (10, 52). Impaired cerebral oxygenation must, therefore, be preceded by substantial and measurable autoregulatory failure. This was not found in our patients. One last possibility is that many of the symptoms thought to be attributable to cerebral hypoperfusion may occur in patients with POTS in whom cerebral perfusion is entirely normal. Many patients with POTS seem to have heightened somatic vigilance and catastrophic cognitions, which may predispose them to increased disability (3). In this regard, it is of interest that, in one-half of the patients, MAST pants inflation did not substantially have symptomatic improvement, despite significant improvement in cardiovascular and cerebrovascular measurements.

In conclusion, this study has shown that the cerebrovascular response, as well as static and dynamic autoregulation during orthostatic stress, was comparable between our cohort of patients with POTS and normal control subjects. Further investigation is required to clarify the underlying pathophysiology of the symptoms that make POTS a disabling condition (2).

GRANTS

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