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ORIGINAL RESEARCH

# Cerebral Blood Flow and Cognitive Performance in Postural Tachycardia Syndrome: Insights from Sustained Cognitive Stress Test

Rachel Wells, MBBS, PhD; Varun Malik, MBBS; Anthony G. Brooks, PhD; Dominik Linz, MD, PhD; Adrian D. Elliott, PhD; Prashanthan Sanders, MBBS, PhD; Amanda Page, PhD; Mathias Baumert, PhD*; Dennis H. Lau, MBBS, PhD*

**BACKGROUND:** The physiology underlying "brain fog" in the absence of orthostatic stress in postural tachycardia syndrome (POTS) remains poorly understood.

**METHODS AND RESULTS:** We evaluated cognitive and hemodynamic responses (cardiovascular and cerebral: heart rate, blood pressure, end-tidal carbon dioxide, and cerebral blood flow velocity (CBFv) in the middle cerebral artery at baseline, after initial cognitive testing, and after (30-minutes duration) prolonged cognitive stress test (PCST) whilst seated; as well as after 5-minute standing in consecutively enrolled participants with POTS (n=22) and healthy controls (n=18). Symptom severity was quantified with orthostatic hypotensive questionnaire at baseline and end of study. Subjects in POTS and control groups were frequency age- and sex-matched (29±11 versus 28±13 years; 86 versus 72% women, respectively; both $P \geq 0.4$). The CBFv decreased in both groups (condition, $P=0.04$) following PCST, but a greater reduction in CBFv was observed in the POTS versus control group (–7.8% versus –1.8%; interaction, $P=0.038$). Notably, the reduced CBFv following PCST in the POTS group was similar to that seen during orthostatic stress (60.0±14.9 versus 60.4±14.8 cm/s). Further, PCST resulted in greater slowing in psychomotor speed (6.1% versus 1.4%, interaction, $P=0.027$) and a greater increase in symptom scores at study completion (interaction, $P<0.001$) in the patients with POTS, including increased difficulty with concentration. All other physiologic responses (blood pressure and end-tidal carbon dioxide) did not differ between groups after PCST (all $P>0.05$).

**CONCLUSIONS:** Reduced CBFv and cognitive dysfunction were evident in patients with POTS following prolonged cognitive stress even in the absence of orthostatic stress.

**Key Words:** cerebral blood flow ■ cognitive dysfunction ■ orthostatic intolerance ■ postural tachycardia syndrome ■ transcranial doppler

Individuals with postural tachycardia syndrome (POTS) often experience several debilitating cardiovascular, gastrointestinal, and neuropsychologic symptoms in addition to their intolerance to standing.[1] Although it is clear that symptoms are related to the assumption of upright posture in these individuals, a myriad of factors that reduce blood volume or decrease vascular tone (such as hot environments, large meals, physical exertion, cardiac deconditioning, and medications) are known to exacerbate POTS symptoms and interfere with activities of daily living.[2–5] The impact of these symptoms on quality of life and cognitive dysfunction has been well described, however, effective treatment options remain limited.[6] Correction of dehydration,

Correspondence to: Dennis H. Lau, Department of Cardiology, Centre for Heart Rhythm Disorders, Royal Adelaide Hospital, Port Road, Adelaide, SA 5000 Australia. E-mail: dennis.h.lau@adelaide.edu.au

*Prof. Baumert and Prof. Lau contributed equally to this work.

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## CLINICAL PERSPECTIVE

### What Is New?

- Compared with age- and sex-matched healthy controls, patients with postural tachycardia syndrome demonstrated greater reduction in cerebral blood flow velocity and psychomotor speed following prolonged cognitive stress testing even in the absence of orthostatic stress.
- The reduction in cerebral blood flow velocity in the middle cerebral artery of patients with postural tachycardia syndrome was similar during prolonged cognitive stress testing and after 5 minutes of standing.

### What Are the Clinical Implications?

- Our findings may explain the common description of 'brain fog' in patients with postural tachycardia syndrome and provide further strength to the concept that cognitive dysfunction in postural tachycardia syndrome represents a consequence of the disease pathophysiology.
- Further studies are needed to delineate the pathophysiological mechanisms underlying these observations.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **CBFv** | cerebral blood flow velocity |
| **$ETCO_2$** | end-tidal carbon dioxide |
| **HR** | heart rate |
| **ICT** | initial cognitive test |
| **PCST** | prolonged cognitive stress test |
| **POTS** | postural tachycardia syndrome |
| **RT** | reaction time |
| **TCD** | transcranial Doppler |

exercise training, and manipulation of vasoactive and heart rate (HR) slowing medications may provide some symptomatic relief, however, improvement in therapeutic approach will require a better understanding of the underlying heterogeneous pathophysiology.[6–10]

Cognitive dysfunction in patients with POTS is sometimes attributed to concurrent anxiety and depression, although performance in tasks requiring sustained attention and short-term memory has also been shown to deteriorate with orthostatic stress.[11,12] The association of cognitive dysfunction with upright posture may relate to a reduction in cerebral blood flow (CBF) or oscillations in blood pressure (BP) and CBF velocity (CBFv).[12,13] However, the persistence of mental fatigue and cognitive disturbances ("brain fog") even in a recumbent position, have been reported in POTS.[14] It remains unclear whether these symptoms can be explained by abnormal cerebral perfusion in the absence of orthostatic stress. We therefore hypothesized that CBFv is reduced in patients with POTS when they are subjected to prolonged cognitive stress performed in the seated position, akin to during orthostatic stress.

## METHODS

We evaluated cognitive and hemodynamic responses (cardiovascular and cerebral) at baseline, after initial cognitive testing and after a 30-minutes duration prolonged cognitive stress test (PCST) whilst seated, as well as after orthostatic stress (5-minute standing) in consecutively enrolled participants with POTS (POTS group, Figure 1). We compared these with a cohort of frequency age- and sex-matched healthy participants (control group). This study was approved by the institutional human research ethics committee and conformed to the Declaration of Helsinki. All participants provided written, informed consent before their inclusion in the study. The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Study Eligibility and Enrollment

Individuals with POTS were enrolled from our autonomic clinic, where specific clinical criteria were met: symptoms produced by upright posture with resolution when recumbent for at least 6 months in duration, as well as documentation of a sustained increment of HR of >30 bpm during head-up tilt testing or within 10 minutes of standing, without a postural BP drop of >20 mm Hg. These symptoms included light-headedness, headache, fatigue, neurocognitive deficits, palpitations, nausea, altered vision, or shortness of breath while upright, with no other medical explanation for the symptoms. All patients with POTS were on treatment in accordance with current guidelines.[7] There were no clinical exclusion criteria. The control group consisted of age- and sex-matched healthy volunteers with no known cardiac or autonomic symptoms.

### Patient Preparation

All testing sessions were performed in the morning, with patients abstaining from alcohol and caffeine over the preceding 24 hours. No changes were made to POTS treatment in the preceding month. Participants were permitted to continue all their usual medications except for vasopressors. Patients who usually took midodrine (α-adrenergic agonist, half-life of 3 hours) in the morning were asked to delay this dose until after completing the study, allowing an interval of at least 15 hours (5x half-life) to elapse from the last dose, to avoid exogenous vasopressor therapy confounding

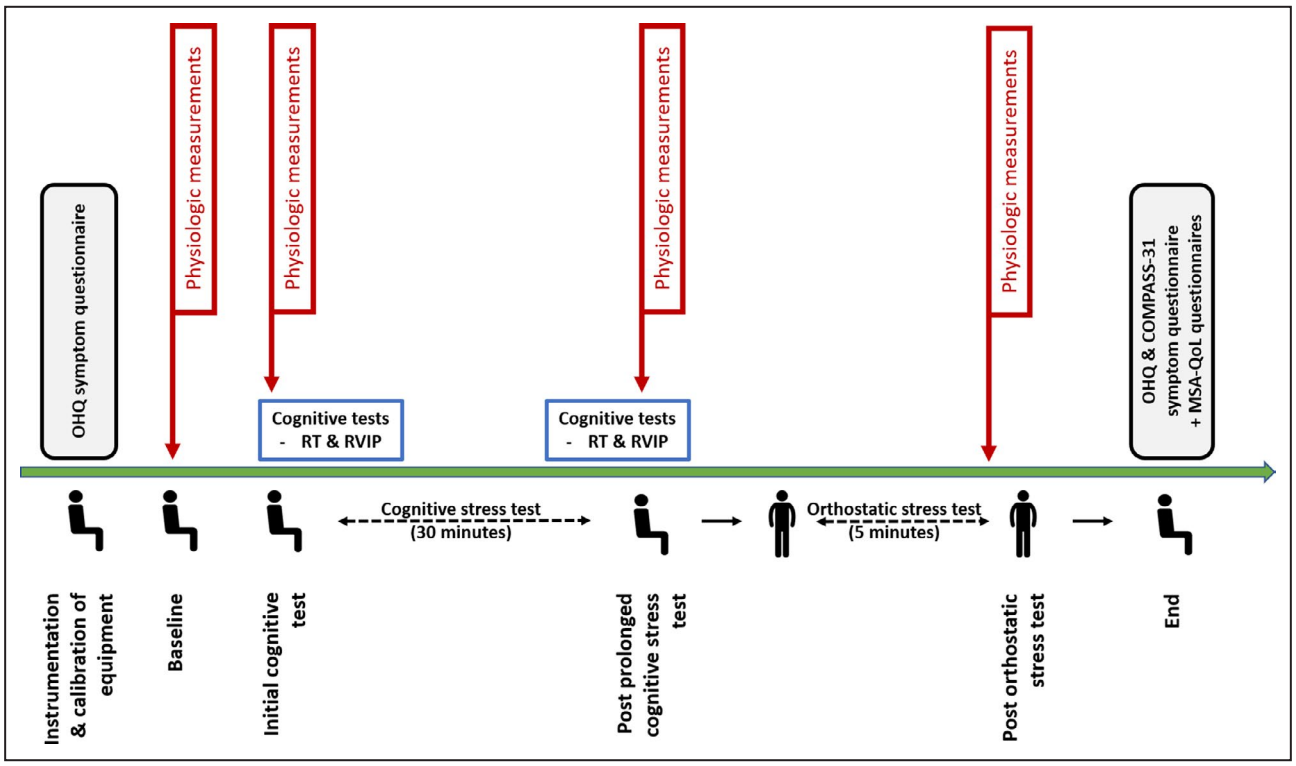


**Figure 1. Study schema.**
Sequence of physiologic and cognitive measurements during the entire study protocol. RT indicates reaction time; RVIP, rapid visual information processing; OHQ, orthostatic hypotension questionnaire; COMPASS-31, composite autonomic symptom score-31; and MSA-QoL, Quality of Life Assessment in Multiple System Atrophy.

interpretation of the study results. The study protocol was performed in a climate-controlled facility (22°C), with participants seated with back support at a desk, emulating normal (school or clerical) working conditions.

## Physiological Measurements

We used transcranial Doppler (TCD) to measure CBFv from the middle cerebral artery of the dominant hemisphere (Doppler-BoxX, Compumedics DWL, Singen, Germany). A 2-MHz transducer probe (PW, Compumedics DWL) was fixed in place over the transtemporal window using adjustable headgear (DiaMon, Compumedics DWL) to minimize movement of the probe during the study protocol. CBFv was recorded continuously throughout the study protocol. A single-lead ECG (FE132 Bioamp, ADInstruments Pty Ltd, NSW, Australia) was placed for continuous monitoring. Continuous, noninvasive beat-to-beat hemodynamics (HR, BP) were also obtained using a cuff placed on the finger (photoplethysmography; Finapres Medical Systems BV, Enschede, The Netherlands). A chest wall strain gauge (MLT 1132/D Piezo Respiratory Belt Transducer, ADInstruments) was used to measure respiratory rate. Lastly, end-tidal carbon dioxide ($ETCO_2$) was measured (Capnostream 20P, Medtronic, Minneapolis, MN, USA) via nasal prongs with mouth scoop (Smart CapnoLine Plus, Microstream, Medtronic). The CBFv wave envelope, ECG, beat-to-beat BP waveform and HR, $ETCO_2$, and respiratory rate data were all recorded simultaneously through a data acquisition device (Powerlab PL35/16, ADInstruments) connected to a personal computer using data acquisition software (LabChart 8, ADInstruments). All data were exported to MATLAB (MathWorks, Natick, MA, USA) for further analysis.

## Neurocognitive Assessment

We performed cognitive testing using an iPad-based (Apple Inc., Cupertino, CA, USA) software collection tool (Cambridge Neuropsychological Test Automated Battery [CANTAB]; Cambridge Cognition, Cambridge, UK).[15] Specifically, we assessed the cognitive domains of psychomotor speed and attention by measuring reaction time (RT) and rapid visual information processing, respectively. In brief, the RT test measures the time taken to release an on-screen button and touch a target in response to a programmed visual stimulus. It measures the speed of both motor and mental response. The rapid visual information processing task assesses the subject's ability to identify a target sequence from a series of numbers that flash up in a pseudo random order onto the iPad screen at a rate of

100 numbers per minute as a measure of sustained attention. Both RT and rapid visual information processing were measured at baseline and after 30 minutes of PCST (Figure 1). The 2 Cambridge Neuropsychological Test Automated Battery tasks used to produce cognitive stress were: delayed matched samples task, which involves recall of complex patterns, and attention switching task, which requires a motor response to rapid visual changes in the position and direction of an arrow that appears on the screen.

## Symptom Assessment

To assess acute changes in symptoms we asked participants to rate their symptoms using the Orthostatic Hypotension Questionnaire with the Likert scale (from 0–10; least to most severe), at baseline and after the prolonged cognitive stress testing.[16] The symptoms assessed were: dizziness, light-headedness or feeling faint; problems with vision (blurring, seeing spots, tunnel vision); weakness; fatigue; trouble concentrating; and head and neck discomfort. While the orthostatic hypotension questionnaire refers to symptoms experienced over the preceding week, we adapted it to assess immediate symptoms.

In addition to assessing current symptoms, all participants were also asked to complete questionnaires at completion of all physiologic measurements to determine their quality of life and autonomic symptoms in the preceding month. A questionnaire to assess quality of life specifically in POTS is not available. The Quality of Life Assessment in Multiple System Atrophy questionnaire was used to assess quality of life, which has been well validated as a patient-reported outcomes tool.[17] Further, autonomic symptoms were assessed using the well validated, abbreviated composite autonomic symptom score-31).[18]

## Statistical Analysis

Normally distributed variables were presented as mean±SD while non-normally distributed variables were presented as median and interquartile range (Q1, Q3). Categorical variables were expressed as numbers and percentages. We used averaged physiologic data over 30 s at the following time points for comparison: at baseline whilst seated, whilst undertaking the initial cognitive testing (ICT) and undertaking repeat cognitive testing after 30 minutes of PCST whilst seated, and during the 5-minute stand test. A mixed effects model was used to assess group (POTS, controls) and condition (baseline versus ICT, ICT versus post PCST, baseline versus orthostatic stress) as main effects and the interaction between group and condition. Individual patient was modeled as random effect to account for repeated measures within individuals between the conditions. Model residuals were visually inspected for normality to ensure an appropriate model fit. Statistical tests were performed using SPSS Statistics (version 24, IBM Corp, Armonk, NY, USA) and statistical significance was set at $P<0.05$.

# RESULTS

## Baseline characteristics

We enrolled 40 participants with POTS (n=22) and healthy sex- and age-matched controls (n=18). Baseline characteristics such as medication usage, seated physiologic and CBF parameters are presented in Table 1. Of the 22 patients with POTS, 6 were taking fludrocortisone, 12 were taking HR control medications (5, ivabradine; 7, propranolol) and 11 were taking midodrine. Notably, the POTS group had higher resting HR whilst seated than the controls (90±14 versus 74±9 bpm; $P=0.010$). There was no difference in mean resting BP, respiratory rate, $ETCO_2$, and CBFv between the groups whilst seated (Table 1).

## Physiologic Changes With Initial Cognitive Testing

There was a greater increase in mean HR in the POTS group than controls during ICT (9.5 versus 4.4%; interaction, $P=0.014$; Figure 2A). Mean HR was consistently higher in the POTS group (group, $P=0.003$) although a significant increase was seen in both groups (condition, $P<0.001$). All other physiologic responses (BP, $ETCO_2$, and CBFv) did not differ between groups during ICT (interaction, $P$ values all ≥0.2, Table 2) despite significant increases in systolic and diastolic BP (condition, $P<0.001$) and CBFv (condition, $P=0.006$) in both groups (Figure 2B through 2D).

## Physiologic and Cognitive Changes During Repeat Cognitive Testing After PCST

HR response during repeat cognitive testing after PCST was similar between groups (interaction, $P=0.656$, Table 2) with consistent slowing as compared with during ICT (condition, $P=0.042$), although the POTS group maintained higher HR than control group throughout (group, $P=0.005$, Figure 2A). Following PCST, a greater reduction in CBFv was seen in the POTS group than controls (–7.8% versus –1.8%; interaction, $P=0.038$, Table 2 and Figure 2C), although CBFv was lower in both groups on repeat cognitive testing (condition, $P<0.001$). All other physiologic responses (BP and $ETCO_2$) did not differ between groups during initial and repeat cognitive testing after PCST (all interaction, $P\geq0.061$, Table 2, Figure 2B and 2D).

The effects of PCST on psychomotor speed and attention are summarized in Table 2. When repeated cognitive testing was performed following PCST, a longer

**Table 1. Baseline Characteristics**

| | POTS (n=22) | Controls (n=18) | *P* Value |
|---|---|---|---|
| Clinical characteristics | | | |
| Age, y | 29±11 | 28±13 | 0.817 |
| Women, n (%) | 19 (86) | 13 (72) | 0.372 |
| Medications, n (%) | | | |
| • Fludrocortisone<br>• Ivabradine<br>• Propranolol<br>• Midodrine | 6 (27)<br>5 (23)<br>7 (32)<br>11 (50) | 0 (0)<br>0 (0)<br>0 (0)<br>0 (0) | … |
| Physiologic measurements (at rest and seated) | | | |
| Heart rate, bpm | 90±14 | 74±9 | 0.010 |
| Systolic BP, mm Hg | 112±12 | 110± 9 | 0.601 |
| Diastolic BP, mm Hg | 78± 12 | 78±10 | 0.898 |
| Pulse pressure, mm Hg | 34±11 | 32±7 | 0.657 |
| Respiratory rate, *breaths/min*) | 17±3 | 17±3 | 0.732 |
| $ETCO_2$, mm Hg | 35±4 | 36±3 | 0.380 |
| CBFv, cm/s | 63.0±13.9 | 65.3±13.3 | 0.758 |
| Quality of life and symptom scores | | | |
| OHSA (from OHQ) | 19 (16, 24) | 0 (0, 2) | <0.001 |
| COMPASS-31 (adjusted) | 46±14 | 10±10 | <0.001 |
| MSA-QoL | | | |
| • Motor<br>• Non-motor<br>• Emotional<br>Total | 13±10<br>25±9<br>20±11<br>58±25 | 0±1<br>4±5<br>5±9<br>9±13 | <0.001<br><0.001<br><0.001<br><0.001 |

Data are presented as mean±SD or median (Q1, Q3). Orthostatic hypotension symptom assessment is the symptom assessment component of the orthostatic hypotension questionnaire used to quantify symptoms present at the time the questionnaire was completed.[13] Six symptoms are given a score from 0 (symptom not present) to 10 (most severe), with a maximum total score of 60. The composite autonomic symptom score-31 (adjusted) is a validated score calculated from the raw composite autonomic symptom score-31 after applying a weighting that considers the number of points and relative importance of organ systems to the assessment of autonomic dysfunction.[15] A high score indicates greater severity of symptoms related to autonomic dysfunction. The Quality of Life Assessment in Multiple System Atrophy score assesses factors that impact quality of life with a high score indicating significant impairment in quality of life.[14] BP, blood pressure; CBFv, cerebral blood flow velocity; COMPASS-31, composite autonomic symptom score-31; $ETCO_2$, end-tidal carbon dioxide; MSA-QoL, Quality of Life Assessment in Multiple System Atrophy; OHSA, orthostatic hypotension symptom assessment; OHQ, orthostatic hypotension questionnaire; and POTS, postural tachycardia syndrome.

delay in mean RT was seen in the POTS group than controls (6.1% versus 1.4%; interaction, $P$=0.027; Figure 2E). While a significant increase in mean RT was seen in both groups (condition, $P$=0.002), mean RT was consistently longer in the patients with POTS (group, $P$=0.007, Figure 2E). When cognitive testing was repeated after PCST, the increase in the number of correct responses in the rapid visual information processing test did not differ between the POTS and control groups (interaction, $P$=0.108, Table 2) despite significant increase in both groups (condition, $P$<0.001; Figure 2F) and consistently lower accuracy in the POTS group (group, $P$=0.05).

## Physiologic Changes at End of 5-Minute Orthostatic Stress

The extent of changes in all physiologic parameters (HR, BP, $ETCO_2$, and CBFv) did not differ between groups from baseline to the end of 5-minute orthostatic stress (interaction $P$≥0.5, Table 2). Orthostatic stress resulted in significant increases in HR (condition, $P$<0.001), systolic BP (condition, $P$=0.001) and diastolic BP (condition, $P$<0.001) as well as a significant decrease in CBFv (condition, $P$=0.002) in both groups (Figure 3A through 3D). Notably, HR was consistently higher in patients with POTS (group, $P$=0.002; Figure 3A) while the remaining physiologic parameters were similar between POTS and control groups (group, $P$≥0.3).

## Symptom and Quality of Life Assessments

Overall quality of life scores (Quality of Life Assessment in Multiple System Atrophy) and symptom scores (composite autonomic symptom score-31) were significantly higher in the POTS group

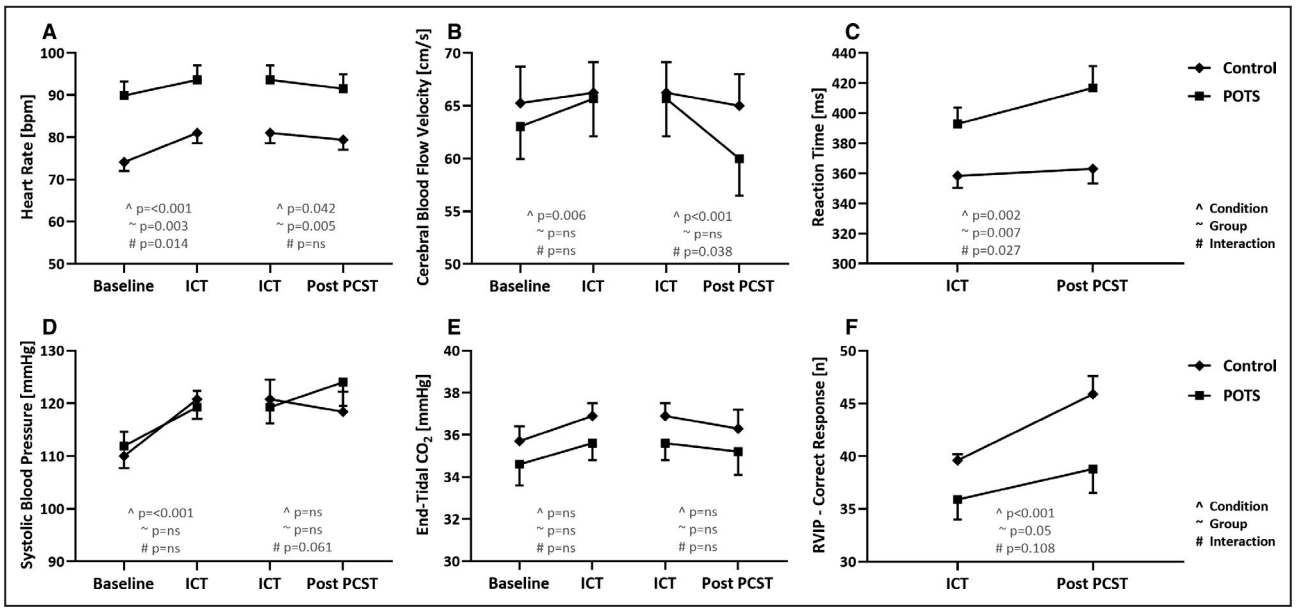


**Figure 2. Physiologic and cognitive parameters with cognitive challenges.**
Changes in (**A**) heart rate; (**B**) systolic blood pressure; (**C**) cerebral blood flow velocity; (**D**) end-tidal carbon dioxide; (**E**) reaction time, and (**F**) number of correct responses with rapid visual information processing, with initial cognitive test and prolonged cognitive stress test are illustrated with the *P* values in each graph denoting comparisons for: *condition (baseline vs initial cognitive test or initial cognitive test vs post prolonged cognitive stress test) in both groups, †group (postural tachycardia syndrome vs control), and ‡interaction (between condition and group). For ease of illustration, all values plotted are mean±SE of the mean with unidirectional error bars. POTS indicates postural tachycardia syndrome; ICT, initial cognitive test; PCST, prolonged cognitive stress test; and RVIP, rapid visual information processing.

in comparison with the control group (Table 1). All patients with POTS described significant symptom burden over at least 6 months with impaired quality of life in motor, non-motor, and emotional components. Specifically, all patients with POTS described slowness of thinking and difficulty with concentration per the Quality of Life Assessment in Multiple System Atrophy questionnaire, with slight, moderate, marked, and extreme difficulty described by 3, 4, 9, and 6 subjects, respectively. In contrast, 12 controls described no difficulty concentrating, while the remaining 6 indicated slight difficulty. At baseline, orthostatic hypotensive symptoms were significantly higher in the POTS versus control groups ($P<0.001$, Table 1). The POTS group demonstrated consistently worse orthostatic symptoms ($P<0.001$) with a significant increase in OHSA scores at the end of the entire research protocol in both groups ($P<0.001$) although the extent of increase was greater in the POTS group [median, 35 (31, 42) versus 3 (1, 8) or +16 versus +3 points, $P<0.001$]. Specifically, following PCST and orthostatic stress test, all but 2 of the patients with POTS rated worsening symptom of "trouble concentrating" with a median increase of 3 (1, 4) points on the Likert scale. In contrast, only 9 of 18 control subjects reported increased symptom of "trouble concentrating" with a median increase of only 0 (0, 2) points ($P<0.001$).

## DISCUSSION

To our knowledge, this study is the first to evaluate CBFv in individuals with POTS undergoing sustained cognitive challenge whilst seated. We found that following PCST, individuals with POTS demonstrate cognitive dysfunction of reduced psychomotor speed which was accompanied by a significant reduction in CBFv when compared with healthy controls whilst remaining seated in the absence of hyperventilation.[19] Additionally, we found that both groups demonstrated similar reductions in CBFv and increments in HR following orthostatic stress of 5 minutes duration. Interestingly, the CBFv following PCST in the POTS group was not dissimilar to that seen during orthostatic stress. In addition, a greater increase in orthostatic symptoms were reported by the patients with POTS as compared with healthy controls at the completion of the entire study protocol. Taken together, the decline in CBFv in seated individuals with POTS during repeat cognitive testing following PCST may explain the common symptom of mental clouding (brain fog) in this patient population.

### CBF and Cognition in POTS

Systemic BP and HR can vary enormously during periods of physical stress and orthostasis. It has been postulated that patients with POTS are unable to adequately buffer

**Table 2. Physiologic and Cognitive Parameters With Cognitive and Orthostatic Challenges**

| | POTS (n=22) | | | Controls (n=18) | | | | |
|---|---|---|---|---|---|---|---|---|
| | Cognitive Challenges | | | | | | | |
| | Baseline | Initial Cognitive Testing | Post Prolonged Cognitive Stress Test | Baseline | Initial Cognitive Testing | Post Prolonged Cognitive Stress Test | *P* Value* | *P* Value |
| Physiologic measurements | | | | | | | | |
| Heart rate, bpm | 90±14 | 94±15 | 92±15 | 74±9 | 81±10 | 79±10 | 0.014 | 0.656 |
| Systolic BP, mm Hg | 112±12 | 119±14 | 124±19 | 110±9 | 121±15 | 118±16 | 0.321 | 0.061 |
| Diastolic BP, mm Hg | 78±12 | 84±11 | 87±16 | 78±10 | 86±11 | 85±14 | 0.168 | 0.137 |
| Pulse pressure, mm Hg | 34±11 | 35±12 | 37±12 | 32±7 | 35±13 | 34±11 | 0.816 | 0.230 |
| $ETCO_2$, mm Hg | 35±4 | 36±4 | 35±5 | 36±3 | 37±3 | 36±4 | 0.911 | 0.855 |
| CBFv, cm/s | 63.0±13.9 | 65.1±15.5 | 60.0±14.9 | 65.3±13.3 | 66.2±12.0 | 65.0±12.3 | 0.351 | 0.038 |
| Cognitive measurements | | | | | | | | |
| Reaction time, ms | … | 393±48 | 417±63 | … | 358±32 | 363±40 | … | 0.027 |
| RVIP (no. correct responses) | … | 36±9 | 39±10 | … | 40±9 | 46±7 | … | 0.108 |

| | 5-min Orthostatic Stress | | | | |
|---|---|---|---|---|---|
| | Baseline | Post Orthostatic Stress | Baseline | Post Orthostatic Stress | *P* Value‡ |
| Heart rate, bpm | 90±14 | 100±20 | 74±9 | 84±11 | 0.954 |
| Systolic BP, mm Hg | 112±12 | 122±21 | 110±9 | 118±13 | 0.571 |
| Diastolic BP, mm Hg | 78±12 | 90±18 | 78±10 | 86±9 | 0.484 |
| Pulse pressure, mm Hg | 34±11 | 32±12 | 32±7 | 31±8 | 0.986 |
| $ETCO_2$, mm Hg | 35±4 | 34±4 | 36±3 | 35±4 | 0.819 |
| CBFv, cm/s | 63.1±13.9 | 60.4±14.8 | 65.3±13.3 | 62.9±11.8 | 0.645 |

BP indicates blood pressure; CBFv, cerebral blood flow velocity; $ETCO_2$, end-tidal carbon dioxide; RVIP, rapid visual information process; and POTS, postural tachycardia syndrome; Data are presented as mean±SD.
*Interaction *P* value between postural tachycardia syndrome and control groups from baseline to initial cognitive testing.
†Interaction *P* value between postural tachycardia syndrome and control groups from initial cognitive testing to post prolonged cognitive stress test.
‡Interaction *P* value between postural tachycardia syndrome and control groups from baseline to 5-minute standing.

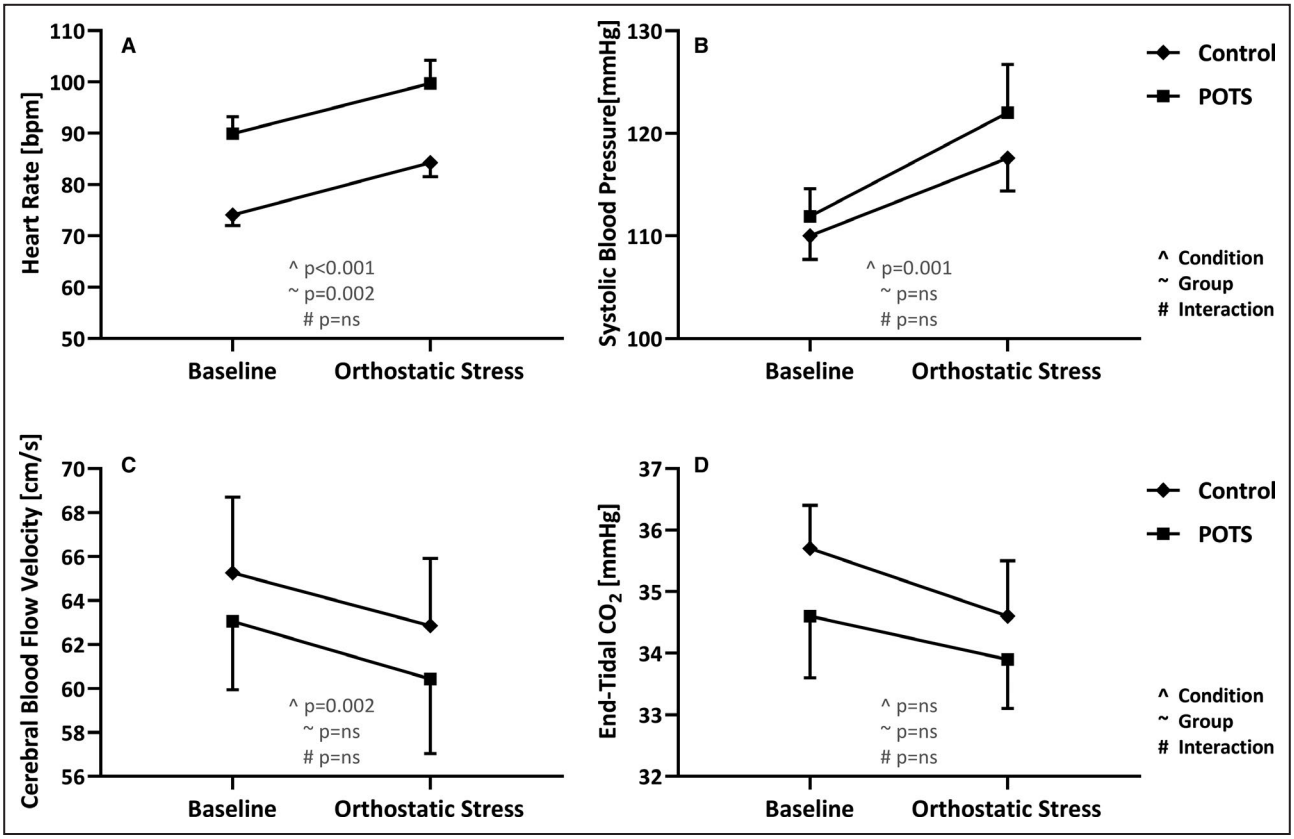


**Figure 3. Physiologic changes with 5-minute orthostatic stress.**
Changes in (**A**) heart rate; (**B**) cerebral blood flow velocity; (**C**) systolic blood pressure; and (**D**) end-tidal carbon dioxide with orthostatic stress are illustrated with the *P* values in each graph denoting comparisons for: *condition (baseline vs orthostatic stress) in both groups, †group (postural tachycardia syndrome vs control) and ‡interaction (between condition and group). For ease of illustration, all values plotted are mean±SE of the mean with unidirectional error bars. POTS indicates postural tachycardia syndrome.

changes in the systemic circulation without compromising cerebral perfusion, termed autoregulation.[20] Several studies have evaluated the effect of orthostatic stress on cognitive function and cerebral hemodynamics in patients with POTS. Ocon et al found a decline in cognitive performance occurring with increasing orthostatic stress in patients with POTS and comorbid chronic fatigue syndrome as compared with controls, that could not be explained by reduced CBFv.[21] In patients with chronic fatigue syndrome and POTS, Stewart et al found that CBF failed to increase with cognitive activity during orthostatic stress while vasomotor tone remained elevated, suggesting an uncoupling of the neurovascular unit.[22] During progressive orthostasis in patients with POTS, increasing oscillatory CBF has been shown to be associated with memory deterioration and reduced neurovascular coupling.[12]

While the above studies have elegantly highlighted the complexities of cerebral hemodynamic response during orthostatic stress in relationship with cognitive function in individuals with POTS, the extent to which these findings could be attributable to co-existing chronic fatigue syndrome is not known.[23] Further, it remains unclear whether patients with POTS have the capacity to increase cerebral perfusion in response to increased cerebral metabolic demand in the absence of orthostatic stress. Others have shown that individuals with POTS encounter cognitive difficulties even when recumbent.[14] In a recent study, we found both short-term memory and alertness were impaired in patients with POTS whilst seated, despite demonstrating similar CBFv response to transient visual stimuli in the posterior cerebral artery when compared with healthy controls.[24] The current study provides additional insights towards cognitive dysfunction in the POTS population. Our findings suggest that in response to sustained cognitive demand, patients with POTS demonstrate reduction in CBFv to a similar degree as during orthostatic stress.

Furthermore, these changes in CBFv during PCST in the POTS group were seen in conjunction with reduced psychomotor speed and subsequent increase in orthostatic symptom severity including increased difficulty with concentrating, a key descriptor of brain fog, as compared with heathy controls. These are in keeping with a previous study in which deficits in selective attention, cognitive processing, and executive function were demonstrated in patients with POTS undertaking

cognitive assessment whilst seated.[14] However, the mechanisms underlying brain fog are likely to be multifactorial, as reported triggers also include lack of sleep and general fatigue, in the absence of orthostatic or cognitive stress.[25]

## Clinical Implications

Our findings lend further strength to the concept that cognitive dysfunction in POTS represents a consequence of the disease pathophysiology. However, further studies are needed to delineate the mechanisms underlying these observations. The use of TCD to measure CBF in the middle cerebral artery has been validated against functional magnetic resonance imaging measures of flow velocities, however, TCD requires a high level of experience to obtain consistently high-quality measures.[26] Nevertheless, TCD measures of CBF may be used as an objective tool to quantitate physiologic states in relationship to objective cognitive and psychological assessments in clinical practice.[27] Whether reduced CBFv is a useful biomarker in the management of POTS remains to be determined.

## Study Limitations

TCD measures CBFv as opposed to CBF. The measures are only equivalent if the vessel diameter does not vary. We did not assess middle cerebral artery diameter during the study, but others have previously observed only minor changes (<4%) in its diameter in response to hypocapnia and changes in BP.[28] We measured CBFv to the dominant cerebral hemisphere. While there is evidence that CBF is comparable between hemispheres during orthostatic stress, CBF may vary between hemispheres during cognitive tasks.[21,29] Undertaking the study with participants in a supine position would have removed the degree of orthostatic stress associated with sitting but would have hampered performance of the PCST and introduced additional noise to CBFv recordings. We acknowledge that our results might be impacted by allowing our patients with POTS to continue their medications with reduced sympathetic activation (in the case of beta-blockade) or impaired concentration (in the case of anti-anxiety or anti-depressant medications). However, withholding these agents could result in rebound tachycardia and impair cognitive performance through sleep deprivation and mental health consequences. The usage of questionnaires to gauge quality of life and orthostatic symptoms are subjected to self-reporting bias.

# CONCLUSIONS

Reduced CBFv and cognitive dysfunction were evident in patients with POTS following prolonged cognitive stress in the seated position. The commonly described symptom of brain fog in POTS is likely attributable to the underlying disease pathophysiology which remains poorly understood.

## ARTICLE INFORMATION

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### Affiliations

From the Centre for Heart Rhythm Disorders, The University of Adelaide, Adelaide, Australia (R.W., V.M., A.G.B., D.L., A.D.E., P.S., M.B., D.H.L.); Department of Medicine (R.W.) and Department of Cardiology (V.M., D.L., P.S., D.H.L.), Royal Adelaide Hospital, Adelaide, Australia; Centre for Nutrition and Gastrointestinal Diseases (A.P.) and School of Electrical and Electronic Engineering, The University of Adelaide, Adelaide, Australia (M.B.).

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