Decreased Upright Cerebral Blood Flow and Cerebral Autoregulation in Normocapnic Postural Tachycardia Syndrome

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Running Head: Decreased Cerebral Blood Flow in Normocapnic POTS

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Abstract

The postural tachycardia syndrome (POTS), a chronic form of orthostatic intolerance, has signs and symptoms of lightheadedness, loss of vision, headache, fatigue, and neurocognitive deficits consistent with reductions in cerebrovascular perfusion. We hypothesized that young, normocapnic POTS patients exhibit abnormal cerebral autoregulation (CA) that results in decreased static and dynamic cerebral blood flow autoregulation. All subjects had continuous recordings of mean arterial pressure (MAP) and cerebral blood flow velocity (CBFV), using transcranial Doppler sonography, both supine and during a 70° head-up tilt. During tilt, POTS patients (n=9) demonstrated a higher heart rate than controls (n=7) (109 ± 6 vs. 80 ± 2 bpm, p < 0.05); whereas controls demonstrated a higher MAP than POTS (87 ± 2 vs. 77 ± 3 mmHg, p < 0.05). Also during tilt, mean CBFV decreased 19.5 ± 2.6 % in POTS vs. 10.3 ± 2.0% in controls (p < 0.05). We then used transfer function analysis of MAP and CBFV in the frequency domain to quantify these changes. The low frequency (LF, 0.04-0.15 Hz) component of CBFV variability increased during tilt in POTS (supine: 3 ± 0.9 vs. tilt: 9 ± 2, p < 0.02). In POTS patients, there was an increase in LF and high frequency coherence between MAP and CBFV, an increase in LF gain, and a lack of significant change in phase. Static CA may be less effective in POTS compared to controls since immediately following tilt, CBFV decreased more in POTS, was highly oscillatory, and autoregulation did not restore CBFV to baseline values until the subjects became supine. Dynamic CA may be less effective in POTS because MAP and CBFV during tilt became almost perfectly synchronous. We conclude that dynamic and static autoregulation of cerebral blood flow are less effective in POTS patients compared with control subjects during orthostatic challenge.
Introduction

The postural tachycardia syndrome (POTS) is a chronic form of orthostatic intolerance (OI). Upon standing upright, patients experience symptoms of OI including lightheadedness, loss of vision, nausea, headache, fatigue, mental cloudiness, hyperpnea, and splanchnic blood pooling (29; 38). POTS often affects adolescents and young adults and is more often seen in females (1; 29). Symptoms are associated with an excessive postural tachycardia, which occurs within 10 minutes of becoming upright. In adults, this is defined by an increase in heart rate (HR) of more than 30 beats per minute (bpm), or a HR that exceeds 120 bpm. Systolic blood pressure is usually maintained. Symptoms of OI such as lightheadedness, loss of vision, headache, fatigue, and neurocognitive deficits are consistent with reductions of cerebral perfusion.

A decrease in cerebral blood flow (CBF) upon becoming upright may produce cerebral hypoperfusion (22; 27; 32; 50). It is controversial whether cerebral blood flow velocity (CBFV) decreases or remains unchanged in POTS patients when they become upright (23; 27; 42). Further, POTS patients represent a heterogeneous group of patients (29; 38; 41). The discrepancies between studies may be due to factors such as age, methodology, and levels of CO₂ due to hyperventilation, all of which have been shown to affect CBFV (24; 34). Also, not all studies reported ETCO₂ values. Furthermore, a subset of POTS patients demonstrates symptoms of hyperventilation and hypocapnia, while another subset exhibits normal ventilation and eucapnia (47). Additional research controlling for these factors while critically delineating subject selection criteria is required to rule out the possibility of decreased CBFV.

If cerebral hypoperfusion does occur in POTS, it would suggest that cerebral autoregulation (CA) may be disrupted. CA describes the phenomenon in which cerebral blood vessels maintain a constant flow through a range of blood pressures by moderating resistance
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Static CA describes the response of the brain to long-term gradual alterations in blood pressure (BP); dynamic CA describes the response of the brain to rapid alterations in BP (15; 54). Altered static CA could mean that POTS patients have a different range of autoregulatory pressures. Altered dynamic CA would mean that POTS patients have difficulty appropriately compensating for quick fluctuations in pressure. Analyses of CA responses often use frequency domain transfer function methods to describe and relate interactions between mean arterial pressure (MAP) and CBFV (10; 15; 26; 27; 42; 59).

To obviate the influences of CO₂ on CBF and CBFV, a study of normocapnic POTS patients is necessary. No prior studies have determined autoregulatory changes in the strictly defined subgroup of young, normocapnic POTS patients. Furthermore, cerebral hypoperfusion may be related to the neurocognitive symptoms experienced by POTS patients. Therefore, we hypothesized that young, normocapnic POTS patients exhibit abnormal cerebral autoregulation that results in decreased static cerebral blood flow (32) and reduced dynamic autoregulation, and that changes may be quantified through transfer function analysis between mean arterial pressure and cerebral blood flow velocity.
Methods

Subjects

As a way to control for influences of CO₂, we only included subjects who maintained normocapnic CO₂ levels (similar to control subjects) during supine and tilt conditions. This implied that subjects maintained unaltered respiratory rates during HUT. Thus, a screening process utilizing analysis of ETCO₂ and respiratory data occurred prior to selection of our subject groups. Out of fifteen consecutive POTS subjects, nine, aged 15-29 years (yrs) old (median age 20.3 yrs, 5 female, 4 male), met these inclusion criteria. Seven consecutive healthy control subjects met these criteria, and were aged 15-29 yrs old (median age 24.4, 4 female, 3 male).

POTS subjects were referred to our center for testing if they experienced symptoms of OI for at least 6 months. POTS was identified during upright tilt table testing to 70° by signs and symptoms of OI and an excessive increase in HR of at least 30 bpm and/or HR exceeding 120 bpm within the first 10 minutes of head-up tilt (HUT) (1; 29; 38; 42). No other medical problems could explain these signs or symptoms. Normocapnia in POTS subjects was defined as an end-tidal CO₂ (ETCO₂) between 35-45 mmHg both supine and during 70° HUT.

Healthy control subjects were defined as individuals having no previously known medical conditions, free of systemic illness, having a normal physical exam and electrocardiogram (ECG), and a normal echocardiogram. Subjects had never experienced OI of any type, including POTS or syncope. Subjects with a history of OI were excluded. Normocapnia in healthy subjects was defined previously in our laboratory; our range of ETCO₂ values are between 35-45 mmHg both supine and during 70° HUT.
Trained athletes, bed-ridden individuals, and individuals who used nicotine-containing products were excluded from enrollment. Subject with a history of asthma, congestive heart disease, renal disease, systemic hypertension, diabetes, acute or chronic inflammatory disease, neoplasm, immune-mediated disease, trauma, morbid obesity, congenital heart disease, peripheral vascular disease, respiratory disease, or other systemic medical problems were also excluded from enrollment. Subject who were pregnant or pregnant in the previous 3 months were excluded. All subjects were required to refrain from all medications for at least 2 weeks prior to the study; however, contraceptive medications were allowed. Seventy-two hours prior to study, all subjects were required to stop ingestion of xanthine-, caffeine-, or alcohol-containing substances. A light breakfast consisting of bread and water was permitted on testing day if it could be eaten 2 or more hours prior to testing. All testing was performed in a single day.

The Institutional Review Board of New York Medical College reviewed and approved this protocol. Each subject received a detailed description of all protocols and was given an opportunity to have their questions answered. Signed informed consent was obtained from all participants.

**Instrumentation**

All subjects were instrumented in a similar fashion by the same operators. Height and weight were measured. During instrumentation, all subjects lay supine on an electronic motorized tilt table (Colin Medical Instruments Corp., San Antonio, TX) with a footboard. Beat-to-beat blood pressure was monitored using finger arterial plethysmography (Finometer; FMS, Amsterdam, The Netherlands) of the right middle or index finger. These data were calibrated to brachial artery pressure. The Finometer contains a sensor that corrects for
height during positional changes, such as tilting. A single lead ECG measured HR. A nasal cannula connected to a capnograph with a pulse oximeter (Smiths Medical, Waukesha, WI) measured ETCO₂. Respirations were measured using a RespiTrace device (NIMS, Inc., North Bay Village, FL). Transcranial Doppler (TCD) (Neurovision; Multigon, Yonkers, NY) measured CBFV of the left middle cerebral artery (MCA) using a 2 MHz probe fixed to the subject’s head by a custom-made headband.

 protocol

All subjects arrived at 9:30 AM. Following instrumentation, subjects remained supine for 30 minutes to acclimate. After acclimation, at least 5 minutes of continuous baseline data were recorded. With completion of supine measurements, 70° HUT testing began. Tilt-testing continued for a maximum of 10 minutes. All subjects in both the POTS and control groups finished the full 10 minute tilt test without any adverse events.

 data analysis

All data were measured continuously and synchronously, and reported values are averages during the time period measured. Signals were converted with an analog-to-digital converter (DI-720 DataQ Ind, Milwaukee, WI) connected to a personal computer and analyzed offline. Following a tilt test, at least the first minute of data were omitted from analysis until each subject stabilized. Mean arterial pressure (MAP) was calculated by the formula MAP = (1/3 * systolic BP) + (2/3 * diastolic BP). To estimate cerebral vascular resistance, the cerebral vascular resistance index, CVRᵢ, where CVRᵢ = MAP/CBFV (4), was used.
Variability Measures and Transfer Function Analyses

Heart Rate and Blood Pressure Variability and Transfer Function

Heart rate variability (HRV) and blood pressure variability (BPV) were analyzed as previously described using autoregression (45; 50). At least 500 beats were acquired during both baseline and HUT measurements. Signals were analyzed for ectopic beats, which were removed using a polynomial curve fitting routine if needed. However, it was rarely necessary to correct for this; other types of arrhythmias were not seen. Data were digitalized at 200 Hz. A custom software package was used to analyze the R-R interval and the MAP as previously described (45; 50). Briefly, an autoregressive model calculated spectral power for the RR interval and mean arterial pressure. The RR interval and MAP was expressed as a sequence of discrete points that was transformed into an impulse train of equal intervals (equal to the mean RR interval). Extended Yule-Walker equations calculated the digital power spectra and Akaike’s final prediction error chose the final order of the model. Spectral power was calculated by taking the power in the actual frequency band and dividing it into a very low frequency (VLF) band (0.01-0.04 Hz), a low frequency (LF) band (0.04-0.15 Hz) and a high frequency (HF) band (0.15-0.40 Hz). Total power was also calculated. For this analysis only LF and HF were used. The alpha index, the ratio of the LF RR interval power to LF BP power, was calculated to express variations in the cardiovagal baroreflex sensitivity (34; 39; 45).

The transfer function was calculated mathematically (3; 59) to obtain coherence, gain, and phase values. Minimum BP-HR coherence values of 0.5 were fulfilled for each subject and prevented inclusion of excessively noisy signals.
The variation between BP and CBFV was measured with a similar method as stated above. CBFV variability (CBFVV) was defined as the variation in the measured CBFV as seen in the frequency domain. MAP and CBFV were analyzed and the transfer function was calculated. Minimum BP-CBFV coherence values of 0.5 were fulfilled for each subject and prevented inclusion of excessively noisy signals. The \( \alpha_{\text{CBF}} \) index, the ratio of the LF MAP power to LF CBFV power, was also calculated.

Coherence, gain, and phase as a function of frequency were applied to describe dynamic cerebral autoregulation in the frequency domain. Coherence describes the synchronization between oscillations in MAP and CBFV. It is the Fourier transform of the cross-covariance. A low degree of synchronization implies strong autoregulation with low coherence because while blood pressure may change blood flow remains constant. Conversely, an increase in synchronization and coherence implies weak autoregulation with a maximum of coherence of 1.0 signifying perfect synchrony between blood pressure and CBF (54). Gain, or magnitude, describes the ratio between the oscillatory amplitudes of MAP and CBFV (54). Phase represents the time lag measured in fractions of an oscillation of MAP and CBFV, with oscillations in CBFV normally preceding changes in MAP (54). An increase in phase is expected upon standing and indicates that MAP and CBF may be falling out of step and thus signifies increasing CA, whereas a decrease in phase approaching zero, is consistent with impaired autoregulation (54).

Higher frequency components of the transfer function represent rapid changes and thus dynamic cerebral autoregulation. Lower frequencies of the transfer function may represent slowly varying cerebrovascular impedance (58).
SPSS 13 software (Apache Software Federation) was used for statistical calculations. Data were compared both during supine and after HUT. SBP, DBP, MAP, HR, ETCO₂, respiration rate, RR interval, CBFV, and CVRi, were analyzed using ANOVA for repeated measures with Bonferroni post-test for multiple comparisons if findings were significant. The nonparametric Mann-Whitney U test was used for to test variability between HR-BP and BP-CBFV because neither was normally distributed. Transfer function coherence, gain, and phase did not follow a normal distribution, and the nonparametric Friedman test was used. Subject age, height, and weight were analyzed using an independent two-tailed t-test. All measures were reported as mean ± SEM. Statistical significance was set at p < 0.05 for all tests.
Results

Subject demographic data

No statistical differences existed between age, height, or weight of the POTS group and control group.

Heart Rate, Blood Pressure, and Cerebral Blood Flow Velocity

Table 1 illustrates the differences in hemodynamic and respiratory values supine and during tilt. While supine, POTS subjects had a lower SBP and a higher HR than controls, although all values were within normal clinical ranges. During HUT, POTS subjects had a decreased SBP and an increased HR compared to controls; whereas, control subjects demonstrated an increased MAP compared to POTS subjects. Figure 1 illustrates that during HUT, mean CBFV decreased 19.5 ± 2.6 % in POTS subjects vs. 10.3 ± 2.0% in controls subjects (p < 0.05). The cerebral vascular resistance index, CVRi, increased in both POTS and control subjects during tilt.

Respiration Rate and End-tidal CO₂

As shown in Table 1, respiration rate did not change significantly in either POTS or control subjects while supine or during HUT. HUT, however, resulted in a decrease in ETCO₂ in both POTS and control subjects to statistically equivalent levels, which remained in the normocapnic range. The range of supine ETCO₂ values for POTS subjects (39-45 mmHg) was not different from the range for controls (40-45 mmHg). Also, during HUT, the range of ETCO₂ values for POTS subjects (37-43 mmHg) was not different from the range for controls (36-43 mmHg) (p > 0.05). The change in ETCO₂ when upright was not different between the two
groups (POTS: 3.5 ± 0.6 vs. control: 2.2 ± 0.8, p = NS). Because a decrease in 1 mmHg of CO$_2$

corresponds to a decrease in CBFV of approximately 3.5% (21; 57), the change in ETCO$_2$ in
POTS during HUT could account for an approximately a 12% decrease in CBFV, while in
controls could it account for an approximately an 8% decrease.

Heart Rate and Blood Pressure Variability and BP-RR Interval Transfer Function Analysis

Table 2 illustrates the values of HRV and BPV obtained while subjects were supine and
upright during HUT. In accordance with previous reports (45; 46), supine and tilt values for
HRV in POTS were significantly lower than control values. Supine, the LF and HF components
of HRV were also lower in POTS than controls. The ratio of the LF to HF components increased
in both groups during tilt. During HUT, only POTS subjects had a significant increase in BPV.
HUT decreased the alpha index in both POTS and control subjects, but it remained significantly
lower in POTS compared to controls.

Also illustrated in Table 2, transfer function analysis demonstrated an increase in LF
coherence in both groups during HUT, while in only POTS subjects HF coherence decreased
significantly. Tilting decreased the LF gain in both groups, but the decrease was significantly
greater in POTS than controls. HF gain decreased in both groups upon tilt. HF phase during tilt
was increased in both POTS and controls but was significantly greater in POTS.

Blood Pressure Variability and Cerebral Blood Flow Velocity Variability

Table 3 shows the changes in blood pressure variability (BPV) and cerebral blood flow
velocity variability (CBFVV) supine and during HUT. As previously mentioned, BPV
significantly increased during tilt only in POTS subjects. Likewise, the LF component of
CBFVV increased during tilt in POTS only. In both POTS and control, there was an increase in the HF component of CBFV during tilt. The alpha\textsubscript{CBF} index increased significantly only in POTS during tilt.

Static Cerebral Autoregulation

Figure 2 shows the effects of tilt on static cerebral autoregulation (SCA) during the entire HUT period in representative a POTS and control subject. Quantization of data from all subjects shows that immediately following tilt, CBFV decreased (Figure 2 Panel B) in both POTS and control subjects. In POTS, the decrease was larger, CBFV was highly oscillatory, and autoregulation did not restore CBFV to baseline values until the tilt was concluded. In contrast, autoregulation in controls brought CBFV back to baseline levels within approximately 100 sec. and it remained stable at this level thereafter.

Dynamic Cerebral Autoregulation

While supine AP and CBFV were poorly synchronized in the representative POTS and control subjects as shown in Figure 3. AP and CBFV in POTS subjects were almost perfectly synchronous during HUT. Thus, beat-to-beat changes in CBFV passively and synchronously followed beat-to-beat changes in arterial pressure as seen in Panel B of Figure 3. Figure 3 demonstrates that dynamic autoregulation (DCA) is essentially absent and that changes in CBFV passively follow changes in arterial pressure.

DCA was also determined through transfer function analysis of MAP-CBFV variability. Figure 4 shows a transfer function between MAP and CBFV for a representative POTS and control subject while supine and during HUT. Table 3 displays average values for these
measures. While supine, POTS subjects had a lower LF phase shift compared to controls. This suggests that while supine, POTS have a closer temporal relationship between MAP and CBFV, with a decrease in the time lag between the change in BP and the change in CBF than controls. As shown in Figure 5, both POTS and controls had a significant increase in LF coherence. Only POTS subjects had a significant increase in LF gain during tilt. Only POTS subjects exhibited a significant increase in HF coherence during HUT.

Correlations

During HUT, only POTS subjects had a significant correlation between HR and SBP (r = -0.74, p < 0.05), DBP (r = -0.85, p < 0.01), and MAP (r = -0.81, p < 0.01), whereas in controls HR did not significantly correlate with SBP (r = -0.45, p = 0.31), DBP (r = 0.68, p = 0.09), or MAP (r = 0.61, p = 0.14). Also, POTS had a significant correlation between MAP-CBFV LF coherence and SBP (r = -0.779, p < 0.05), DBP (r = -0.704, p < 0.05), and MAP (r = -0.748, p < 0.05). Controls did not have a significant correlation between MAP-CBFV LF coherence and SBP (r = -0.07, p = 0.88), DBP (r = -0.28, p = 0.55), or MAP (r = -0.31, p = 0.49). These correlations are time domain counterparts of the frequency domain variability findings reported above.
Discussion

Summary and Novel Findings

This study demonstrates new findings about cerebral autoregulation in both POTS and healthy control subjects. First, we have shown that in young, normocapnic POTS subjects, CBFV drops by 19.5% compared to only 10.3% in healthy controls during HUT. In POTS subjects, this could not be accounted for by a posturally-induced change in ETCO2 alone because that would only accounted for a 12% decrease. Static autoregulation (i.e. the average change in CBFV at a given arterial pressure) was, therefore, decreased in POTS compared to control subjects and remained decreased throughout the tilt.

Secondly, although transfer function analysis of blood pressure and CBFV implicitly involve computation of cerebral blood flow velocity variability (CBFVV) (58; 59), we are, to our knowledge, first to make explicit use of CBFVV measurements in relation to POTS. These are potentially important because they convey a tangible sense of how much and how rapidly CBF changes. CBFVV, at low frequency, represents the overall effects of cerebrovascular transduction of blood pressure, represented as Mayer waves (11), which appear with increased amplitude during tilt in POTS subjects (Figure 3 Panel B). Mayer waves represent the increase in sympathetic baroreflex activity engendered by orthostasis (31; 35), and this increase in baroreflex activity is increased in POTS (Table 3).

We have additionally demonstrated that during HUT, only POTS subjects show an increase in the LF component of CBFVV, while both POTS and controls show a smaller increase in the HF component. Similarly, the low frequency gain (transfer function amplitude) and alpha_{CBF} index of MAP-CBFV variability increased during HUT only in POTS subjects. We demonstrated that the LF and HF coherence between MAP and CBFV increases during HUT in
both POTS and control subjects, but increased to a greater degree in POTS. Also, the LF
coherece between MAP and CBFV during HUT correlated with SBP, DBP, and MAP only in
POTS subjects. The combination of increased Mayer wave amplitudes, increased gain and
increased coherence at low frequency accounts for the increase in CBFVV. Corresponding
observations were made in the time domain (Figure 3), in which oscillations in AP are nearly
synchronous with oscillations in CBFV. Also, we demonstrated how static and dynamic cerebral
autoregulation are ineffective for maintaining CBFV during tilt.

Implications for POTS Patients

Dynamic and static autoregulation are less effective in young, normocapnic POTS subjects
compared to control subjects during HUT, as demonstrated by the decreased CBFV, increased
LF (0.1Hz) and HF (0.25Hz) coherence between MAP and CBFV, and increased LF gain, with
lack of an associated change in phase differences which remain low. This results in a lower
CBFV with greater CBFVV at low frequency, i.e. greater oscillations in already reduced cerebral
blood flow – signs of both static and dynamic autoregulatory deficits. The frequency of 0.1 Hz
converts to a time scale of 10 seconds, and half of an oscillatory period would be 5 seconds. This
means that CBF is further decreased for 5 seconds and increased for 5 seconds compared to the
reduced static baseline. As a result, substantially lowered CBF occurs 50% of the time in POTS
compared to control when upright, which can impair cerebral perfusion and neurocognitive
function (56). A decrease in perfusion of the brain may help to explain symptoms of
lightheadedness, dizziness, and mental confusion that are common in POTS patients (27; 33; 42).
Dynamically, oscillations in CFBV coincide with oscillations in AP (see Figure 3). Since POTS
exhibited lower MAP than controls, therapies that increase MAP may also increase CBFV,
possibly alleviating the cognitive impairment.

Comparison with the Literature

End-Tidal CO$_2$ and HUT

It is well known that changes in arterial PCO$_2$ levels affect brain blood flow and that CO$_2$
levels decrease during tilt (9). Appropriately, we noted that POTS and control subjects exhibited
a decrease in ETCO$_2$ during tilt. Because respiratory rate does not change with tilt, the decrease
in ETCO$_2$ has been ascribed to changes in the ventilation-perfusion relationship due to wider
expansion of the lower chest wall (9). Furthermore, decreases in ETCO$_2$ values may
overestimate decreases in arterial PCO$_2$ values and should be scrutinized when applied to
changes in CBF (6; 43).

From our results, we show that the change in ETCO$_2$ cannot fully account for the changes
in CBFV. Schondorf et al. (42) studied adult POTS patients and found that ETCO$_2$ values did not
differ during early or late HUT and that POTS patients’ respiratory rates were similar to those of
healthy control subjects. Thus, if ETCO$_2$ did accurately reflect changes in arterial PCO$_2$ during
the duration of the tilt, the maximum effect should be a 12% decrease. This is much less than the
nearly 20% decrease we found, and our conclusion is consistent with the literature (43).

Static Autoregulation: Decreased CBFV during Tilt

We report a 19.5% static decrease in CBFV in POTS subjects during tilt compared to a
10.3% decrease in controls. These results contrast with those observed by Schondorf et al. (42)
who reported that CBFV did not significantly differ between POTS and controls during tilt. This
difference in findings may be due to the difference in age groups of each study, different durations of tilt timing, inclusion of hypocapnic test subjects, as well as the heterogeneity between POTS patients. On the other hand, Jacob et al. (22) reported findings similar to ours, with a decrease in CBFV of 28 ± 10% in POTS patients and 10 ± 10% in controls during tilt. Their study included subjects who were older than ours (22-47 years old) and they employed varying degrees of tilt.

Heart Rate-Blood Pressure Variability

We found that HRV in POTS subjects was decreased while supine and when upright but that BPV was increased when upright, compared to control subjects. This is consistent with previous reports (45; 46). The decrease in LF and HF HRV gain (see Table 2) in POTS during HUT is consistent with vagal withdrawal (45). This data suggests that there is intact baroreflex and sympathetic function in young, normocapnic POTS patients. These sympathetic mechanisms may compensate for the decrease in BP in POTS subjects during HUT and may result in the oscillatory changes seen (see Figure 3).

Coherence and Synchronization

Due to the increased coherence and synchronization between MAP and CBFV, we suggest that increased baroreflex mediated fluctuations in pressure may be translated into increased fluctuations (variability) of CBFV. Increased sympathetic activity during HUT in POTS is supported by the report of increased muscle sympathetic nerve activity in POTS compared to controls (31). The increased sympathetic baroreflex activity along with vagal
withdrawal in POTS patients during tilt may play a role in the synchronization between CBFV and MAP (36).

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**Cerebral blood flow velocity variability**

Cerebral blood flow velocity variability (CBFVV) describes the oscillatory changes that occur in CBFV during tilt. We found that the LF components of CBFVV (Table 3) increased only in POTS during HUT. LF components are associated with sympathetic-baroreflex activity; whereas, HF components are associated with parasympathetic-respiratory activity and cerebrovascular impedance, and are less clearly defined physiologically.

The sympathetic-mediated constriction of the MCA is controversial: some investigators found little sympathetic vascular control (4; 44; 48), while others have found a large sympathetic contribution to cerebral blood flow regulation in humans and mammals (7; 55). Bondar et al. (7) states that a sympathetic-mediated vasoconstriction could shift the autoregulatory curve to the right, thus autoregulation would be efficient at high arterial pressures but inefficient at lower pressures. If this occurred, the decrease in arterial pressure seen in POTS during tilt would not be autoregulated, and CBFV would decrease in relation to the decrease in MAP. However, we are unable to say, nor do we intend to imply, that the sympathetic nervous system (SNS) is the main control mechanism regulating CBF in POTS patients. However, the intact baroreflex in POTS patients mediates oscillations in MAP and CBFV. This is supported by Baumbach and Heistad (2) who state that momentary changes in MAP produce similar changes in CBFV. Additional support comes from Birch et al. (5), who suggest that rapid alternation in MAP result in ineffective CA, allowing CBFV to oscillate directly with pressure. The oscillations of MAP are baroreflex mediated, but the responses of cerebral arterioles could relate to actions of the SNS or...
to other mechanisms, such as local, flow-mediated, myogenic, neural, cell signaling, and/or metabolic processes (8; 20; 25; 52).

Cerebral Autoregulation

Cerebral autoregulation is considered a high-pass filter of MAP, such that slow changes in MAP are dampened and rapid changes pass through, thereby causing oscillations in CBFV (26). The range of CA is not inflexible, and pathological states seen in humans, rats, and dogs, such as hypertension (49; 53) or hemorrhage (17), can shift it. Oscillations in CBFV during tilt in POTS have previously been described by Hermosillo et al. (18) who suggested that they may be related to inefficient autoregulation and increased HR. Our data are in accordance with this.

To study static CA, we used the average change in CBFV during tilt (see Figure 2 and Table 1). Others have used CVR, as an index of static CA (42), and reported a decrease in resistance during tilt. This is contrary to what we and others have found (7; 22). Physiologically, the assumption is that cerebral resistance should increase during tilt if cerebral perfusion pressure is being maintained and would decrease if CBF is being maintained. Therefore, CVR, may not be the best index of static CA, as these responses are contradictory and may oppose each other.

Furthermore, during tilt, the brain is rostral to the heart, and systemic MAP may not be representative of cerebral MAP (58). The index has limitations to its accuracy. In relation to this, a normalized gain has been calculated by others based on CVRi (42). Due to the limitations of CVRi, we did not calculate normalized gain.

During tilt, dynamic cerebral autoregulation appears to be impaired in POTS. Dynamically, CBFV oscillations are nearly perfectly synchronous with the oscillations in AP in POTS subjects (see Figure 3). This increase in synchronization is similar to what Birch et al. (5)
report during stand-squat maneuvers in healthy subjects. They also concluded that dynamic CA is ineffective if MAP changes quickly (5).

Additionally, we used transfer function analysis to describe dynamic CA. The increase in both LF and HF coherence (see Table 3 and Figure 4) suggests that oscillations in MAP are directly influencing oscillations in CBFV. Thus, there is a decrease in dynamic autoregulation and the cerebral vasculature is acting like a passive fixed Ohmic resistor. This conclusion is supported by Low et al. (27) and Diehl et al. (12), who also suggest a linear relationship between MAP and CBFV. Recent work by Zhang et al. (10) supports this claim in their study of dynamic autoregulation in healthy subjects. Increased gain suggests that the attenuation of dynamic CA is ineffectively dampening the effects of the oscillations of MAP on CBFV (15; 54). The lack of change in phase shift from supine conditions and the trend that phase decreases through the frequency range studied suggests that dynamic CA is not greatly influencing how oscillations in CBFV are responding to orthostatic conditions. Normally, CBFV leads MAP in phase (54). Phase shifts near zero degrees are considered to represent ineffective CA (26).

**Coherence and Tilt**

Why then is coherence seldom used as the index of [or lack of] dynamic autoregulation? A coherence of 1 implies a perfectly linear relationship between input and output, MAP and CBFV. Most investigators use a coherence of > 0.5 to indicate the potential for any linear time-invariant relationship between two signals. This requirement can be explained by considering the reasons for deviation of coherence from a perfect 1.0. Coherence can be reduced by three main factors. The first is noise (3; 28; 37). The requirement for coherence >0.5 is customarily employed to avoid overly noisy systems. In our data, it is highly unlikely that noise predominates
because upright coherence is so close to 1.0, and because we have no reason to believe that the act of tilting alters noise. Second, nonlinearity of a system can decrease coherence and make it an imperfect measure of synchronization (3; 16; 37). This could certainly be true, but if so, nonlinearity is highly affected by posture, decreasing in the upright position. Last, coherence can be decreased if there are other inputs that are not included in the calculation of coherence (37). We think this is most likely. We propose that while supine, certain input signals influence coherence and that these signals are essentially removed (or greatly lessened) as inputs when upright. Candidates for such input signals include the controversial sympathetic-mediated changes in CBF control which may asymptotically reach a maximal value. However, it is unlikely that sympathetic activity is actually maximized in most POTS patients as this would result in upright heart rates well in excess of those measured. We think a more likely possibility is vagal withdrawal which is nearly complete in POTS patients (with heart rates of > 110 bpm) and only partially present in control subjects (45). This is consistent with CBF dependence on parasympathetic activity. This remains speculative and further work is needed to decipher the exact mechanism(s).

**Limitations**

Transcranial Doppler measures changes in middle cerebral artery blood flow velocity instead of blood flow directly. Velocity and flow are not the same. This method assumes that the diameter of the middle cerebral artery (MCA) does not change during tilting. MRI studies in humans during orthostasis have demonstrated that the MCA diameter remains constant and is not affected by changing levels of CO₂ (13; 44).
Transfer function analysis assumes linearity of a system. Our study assumes linearity between MAP and CBFV as well. This may not always be the case. Panerai et al. (37) suggest that linearity may not always hold, and coherence values may be higher if nonlinearity is taken into account. Mitsis et al. (30) described a nonlinear model of cerebral autoregulation to illustrate changes in cerebral hemodynamics during lower body negative pressure studies. Novak et al. (19) described a “multimodal pressure-flow model” to determine nonlinear cerebral autoregulation between MAP and CBFV in supine subjects. They described CA as phase shifts between MAP and CBFV oscillations in control patients, and also found a high correlation between the phase oscillations of MAP and cerebral perfusion pressure in traumatic brain injury patients (19).

Beat-to-beat continuous blood pressure was monitored using finger arterial plethysmography. With this method, we assume that MAP in the finger is representative of MAP in the brain and that changes in intracranial pressure are insignificant.

Carbon dioxide is well-known to affect CBF. In this study, we attempted to control for this factor by only using POTS and control subjects who exhibited CO₂ levels in the normocapnic range while both supine and during tilt. In both POTS and controls, ETCO₂ levels demonstrated small decreases upon tilt. We are limited by not measuring tidal volume or the overall volume of CO₂ expired. Further, we are limited by not measuring arterial PCO₂ content.

Our subjects were allowed to eat a light breakfast 2 or more hours prior to the experiment. Rowe et al. (40) demonstrated that feeding did not change cerebral blood flow. On a
related note, hypoglycemia does not appear to affect cerebral blood flow until glucose levels are below a concentration (< 2 mmol/L) that would cause noticeable cerebral cognitive impairment (51). Thus, we believe that neither feeding nor fasting confounded our results. On the other hand, we did not standardize blood glucose levels or monitor them, and therefore, we state this limitation.

Our number of control subjects (n = 7) is small and may be questioned as limiting. We believe the small standard errors of the mean may be interpreted as showing the uniformity of the physiological responses tested in these subjects.

Sympathetic nerve function was assessed using LF variability techniques. Respiration influences sympathetic activity (14) and we are limited by not measuring ventilation volumes.

Summary

In summary, we conclude that cerebral blood flow velocity decreases more in POTS subjects than control subjects during tilt. This may be due to altered and inefficient cerebral autoregulation. Decreased cerebral blood flow can impair consciousness and neurocognitive function.
Acknowledgements

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This study was supported by the National Heart, Lung, and Blood Institute Grants R01HL074873-05, 1R21HL091948-01, and 1R01HL087803-01A1 and the American Heart Association Grant 0735603T.
Table 1. Hemodynamic and Respiratory Parameters Supine and Tilt

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Supine</th>
<th>70° HUT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>POTS</td>
<td>Control</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>114 ± 3 #</td>
<td>121 ± 1</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>59 ± 2</td>
<td>61 ± 3</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>78 ± 2</td>
<td>81 ± 2</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>73 ± 3 #</td>
<td>54 ± 3</td>
</tr>
<tr>
<td>ETCO2 (mmHg)</td>
<td>43 ± 1</td>
<td>43 ± 1</td>
</tr>
<tr>
<td>Respiration (min⁻¹)</td>
<td>18 ± 1</td>
<td>17 ± 1</td>
</tr>
<tr>
<td>RR Interval (msec)</td>
<td>821 ± 32 #</td>
<td>1097 ± 42</td>
</tr>
<tr>
<td>Mean CBFV (cm/sec)</td>
<td>70 ± 5</td>
<td>69 ± 6</td>
</tr>
<tr>
<td>CVRi (mmHg/cm/sec)</td>
<td>1.2 ± 0.1</td>
<td>1.3 ± 0.2</td>
</tr>
</tbody>
</table>

Table 1. Value = mean ± SEM. HUT, head-up tilt. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; ETCO2, end-tidal CO2; CBFV, cerebral blood flow velocity; CVRi, cerebral vascular resistance index. * p < 0.05 within group compared to supine values. # p < 0.05 compared to control group.
Table 2. Heart Rate and Blood Pressure Variability Measures

<table>
<thead>
<tr>
<th></th>
<th>Supine</th>
<th>Control</th>
<th>70° HUT</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>POTS</td>
<td>Control</td>
<td>POTS</td>
<td>Control</td>
</tr>
<tr>
<td>HRV</td>
<td>994 ± 153 #</td>
<td>3450 ± 520</td>
<td>707 ± 216 #</td>
<td>2126 ± 663</td>
</tr>
<tr>
<td>HRV - LF</td>
<td>304 ± 45 #</td>
<td>842 ± 182</td>
<td>418 ± 151</td>
<td>588 ± 310</td>
</tr>
<tr>
<td>HRV - HF</td>
<td>433 ± 84 #</td>
<td>1555 ± 395</td>
<td>138 ± 42 *</td>
<td>416 ± 223</td>
</tr>
<tr>
<td>LF/HF</td>
<td>0.9 ± 0.2</td>
<td>0.5 ± 0.1</td>
<td>4 ± 0.8 *</td>
<td>4 ± 1 *</td>
</tr>
<tr>
<td>BPV</td>
<td>11 ± 2</td>
<td>15 ± 4</td>
<td>28 ± 4 *</td>
<td>26 ± 7</td>
</tr>
<tr>
<td>BPV - LF</td>
<td>3 ± 0.5</td>
<td>3 ± 0.8</td>
<td>18 ± 4 *</td>
<td>15 ± 6 *</td>
</tr>
<tr>
<td>BPV - HF</td>
<td>2 ± 0.2</td>
<td>2 ± 1.2</td>
<td>5 ± 0.6 *</td>
<td>4 ± 0.7</td>
</tr>
<tr>
<td>Alpha (ms/mmHg)</td>
<td>12 ± 1 #</td>
<td>17 ± 3</td>
<td>5 ± 0.8 * #</td>
<td>9 ± 1 *</td>
</tr>
<tr>
<td>LF Coherence</td>
<td>0.65 ± 0.03</td>
<td>0.64 ± 0.06</td>
<td>0.78 ± 0.07 *</td>
<td>0.85 ± 0.03 *</td>
</tr>
<tr>
<td>LF Gain (ms/mmHg)</td>
<td>15 ± 1</td>
<td>21 ± 3</td>
<td>4 ± 1 * #</td>
<td>8 ± 1 *</td>
</tr>
<tr>
<td>LF Phase (degrees)</td>
<td>45 ± 5</td>
<td>32 ± 12</td>
<td>56 ± 6</td>
<td>41 ± 5</td>
</tr>
<tr>
<td>HF Coherence</td>
<td>0.83 ± 0.03</td>
<td>0.79 ± 0.03</td>
<td>0.64 ± 0.06 *</td>
<td>0.77 ± 0.04</td>
</tr>
<tr>
<td>HF Gain (ms/mmHg)</td>
<td>15 ± 2</td>
<td>27 ± 5</td>
<td>5 ± 1 *</td>
<td>9 ± 2 *</td>
</tr>
<tr>
<td>HF Phase (degrees)</td>
<td>13 ± 7</td>
<td>2 ± 9</td>
<td>64 ± 7 * #</td>
<td>37 ± 11</td>
</tr>
</tbody>
</table>

Table 2. Values = mean ± SEM. HRV, heart rate variability. HRV – LF, low frequency component of heart rate variability. HRV – HF, high frequency component of heart rate variability. LF/HF, heart rate variability ratio between low frequency and high frequency. BPV, blood pressure variability. BPV – LF, low frequency component of blood pressure variability. BPV – HF, high frequency component of blood pressure variability. LF, low frequency. HF, high frequency. * p < 0.05 within group compared to supine values. # p < 0.05 compared to control group.
### Table 3. Mean Arterial Pressure and Cerebral Blood Flow Velocity Variability Measures

<table>
<thead>
<tr>
<th></th>
<th>Supine</th>
<th>70° HUT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>POTS</td>
<td>Control</td>
</tr>
<tr>
<td>MAPV</td>
<td>5 ± 0.6</td>
<td>7 ± 1</td>
</tr>
<tr>
<td>MAPV – LF</td>
<td>2 ± 0.3</td>
<td>2 ± 0.2</td>
</tr>
<tr>
<td>MAPV – HF</td>
<td>0.8 ± 0.2</td>
<td>0.3 ± 0.1</td>
</tr>
<tr>
<td>CBFVV</td>
<td>10 ± 2</td>
<td>10 ± 2</td>
</tr>
<tr>
<td>CBFVV – LF</td>
<td>3 ± 0.9</td>
<td>3 ± 0.6</td>
</tr>
<tr>
<td>CBFVV – HF</td>
<td>1 ± 0.3</td>
<td>1 ± 0.2</td>
</tr>
<tr>
<td>(\text{Alpha}_{\text{CBF}}) (ms/mmHg)</td>
<td>0.8 ± 0.1</td>
<td>1 ± 0.2</td>
</tr>
<tr>
<td>LF Coherence</td>
<td>0.53 ± 0.04</td>
<td>0.54 ± 0.08</td>
</tr>
<tr>
<td>LF Gain (mmHg/cm/sec)</td>
<td>0.7 ± 0.1</td>
<td>0.7 ± 0.1</td>
</tr>
<tr>
<td>LF Phase (degrees)</td>
<td>39 ± 5 #</td>
<td>64 ± 6</td>
</tr>
<tr>
<td>HF Coherence</td>
<td>0.65 ± 0.04</td>
<td>0.52 ± 0.07</td>
</tr>
<tr>
<td>HF Gain (mmHg/cm/sec)</td>
<td>0.8 ± 0.1</td>
<td>0.7 ± 0.1</td>
</tr>
<tr>
<td>HF Phase (degrees)</td>
<td>15 ± 4</td>
<td>-0.3 ± 6</td>
</tr>
</tbody>
</table>

Table 3. MAPV, mean arterial pressure variability. MAPV – LF, low frequency component of mean arterial pressure variability. MAPV – HR, high frequency component of mean arterial pressure variability. CBFVV, cerebral blood flow velocity variability. CBFVV – LF, low frequency component of cerebral blood flow velocity variability. CBFVV – HF, high frequency component of cerebral blood flow velocity variability. LF, low frequency. HF, high frequency. * \(p < 0.05\) within group compared to supine values. # \(p < 0.05\) compared to control group.
References


Figure 1. Percent change in cerebral blood flow velocity during tilt. POTS subjects, during tilt, exhibited approximately a 20% decrease in CBFV whereas controls exhibited approximately a 10% decrease. CBFV, cerebral blood flow velocity. *p < 0.05 compared to control.
Figure 2. Static autoregulation in a representative POTS and control subject during tilt. Gray represents POTS. Black represents Control. Panel A: Mean arterial pressure (MAP) oscillations during tilt. Panel B: Cerebral blood flow velocity (CBFV) oscillations during tilt. Arrows represent beginning and end of tilt (600 sec. range). POTS CBFV initially falls upon tilting and does not recover until return to supine. Control CBFV initially falls but soon recovers, remaining relatively stable throughout the duration of the tilt.
Figure 3: Dynamic autoregulation in a representative POTS and control subject during supine and tilt.
Panel A: One minute interval of a POTS subject’s arterial pressure (AP) and cerebral blood flow velocity (CBFV) while supine. Panel B: One minute interval of a POTS subject’s AP and CBFV during tilt. Panel C: One minute interval of a control subject’s AP and CBFV while supine. Panel D: One minute interval of a control subject’s AP and CBFV during tilt. While supine, there does not appear to be a strong relationship between AP and CBFV in either POTS or control subjects. During tilt, AP and CBFV become very synchronous in POTS subjects, oscillations in CBFV passively follow oscillations in AP, and dynamic autoregulation is reduced. In control subjects during tilt, AP and CBFV are less synchronous, demonstrating intact dynamic autoregulation.
Figure 4. Frequency domain transfer function of MAP and CBFV for a representative POTS and control subject during supine and tilt. During tilt, there is an increase in low frequency (LF, 0.04-0.15 Hz) coherence between MAP and CBFV in both POTS and controls and an increase in high frequency (HF, 0.15-0.40 Hz) coherence between MAP and CBFV in POTS. During tilt, POTS patients have a significant increase in LF gain. In POTS during tilt, phase tends to decrease and approach zero as frequency increases into the HF range.
Figure 5. Low frequency (LF, 0.04-0.15 Hz) coherence between mean arterial pressure (MAP) and cerebral blood flow velocity (CBFV) in POTS and control subjects during supine and tilt. Gray represents POTS subjects and black represents control subjects. Both POTS and control subjects exhibited an increase in LF coherence during tilt conditions. *p < 0.05 compared to supine measurements.