Improving the evidence base for treatment of Postural Orthostatic Tachycardia Syndrome (POTS)

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Abbreviations

AST	Attention switching task
Bid	twice daily
BP	blood pressure
bpm	beats per minute
CANTAB	Cambridge Neuropsychological Test Automated Battery
CBF	cerebral blood flow
CBFv	cerebral blood flow velocity
CENTRAL	Cochrane Central Register of Controlled Trials
CI	confidence interval
CNHSQ	Children's National Health System Questionnaire
COMPASS	composite autonomic symptom score
DBP	Diastolic blood pressure
EDV	End diastolic velocity
EPO	erythropoietin
ETCO2	End tidal carbon dioxide
FeSo4	ferrous sulfate
fMRI	functional magnetic resonance imaging
HPA axis	hypothalamus-pituitary-adrenal axis
HR	heart rate
HUTT	Head up tilt test
IBS	irritable bowel syndrome
IV	intravenous

IM	intramuscular
IQR	Interquartile range
LAR	long-acting release
MAP	Mean arterial pressure
MCA	middle cerebral artery
MRI	Magnetic resonance imaging
NA	not available
NET	norepinephrine transporter
NIRS	Near infrared spectroscopy
NVC	Neurovascular coupling
OD	once daily
OH	Orthostatic hypotension
OHQ	Orthostatic Hypotension Questionnaire
OHDAS	Orthostatic hypotension daily activity scale
OHSA	Orthostatic hypotension symptom assessment
OI	orthostatic intolerance
PCA	posterior cerebral artery
POTS	posterior orthostatic tachycardia syndrome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSV	Peak systolic velocity
QOL	quality of life
RCT	randomised controlled trial
RR	Respiratory rate
RT	Reaction time

RVIP	Rapid visual information processing
SC	subcutaneous
SCI	Spinal cord injury
SF-36	Short form 36 questionnaire
SQ(n)	symptom questionnaire rating on (n) symptoms
SR	slow release
TAP	Time averaged peak
TCD	transcranial Doppler ultrasound
Tid	3 times per day
WFDI	Walker Functional Disability Inventory
WSS	Winker symptom scale

Thesis Aims and Outline

Postural tachycardia syndrome (POTS) is a chronic debilitating condition characterized by symptoms of light-headedness, fatigue, palpitations, pre-syncope, sleep disturbances, cognitive impairment and brain fog in conjunction with an exaggerated increase in heart rate (HR) when upright, despite maintenance of a normal blood pressure (BP). There is little high-level evidence to inform current guidelines for the investigation and management of POTS, at least in part due to the lack of biological markers to provide clarity on diagnosis and to quantify severity of disease. The objectives of the work described in this thesis was to highlight the gaps in evidence for therapeutic modalities currently available for the treatment of patients with POTS and to study the value of transcranial doppler (TCD) measures of cerebral blood flow velocity (CBFv) during orthostatic and cognitive stress for future therapeutic trials in patients with POTS. The rationale behind use of TCD measurement of CBFv relates to the hypothesis that periodic reduction in cerebral blood flow (CBF) due to inadequate compensation for changes in orthostatic pressure may explain the almost universal symptom of mental clouding described by patients with POTS. Since many patients with POTS describe mental clouding even when recumbent, we hypothesized that regulation of CBF in response to cognitive activation in the absence of orthostatic stress may also be dysfunctional. We therefore studied CBF during both orthostatic and cognitive stress in patients with POTS.

An overview of the pathophysiology and co-morbidities associated with POTS is provided in Chapter 1 followed by a systematic review of the efficacy and quality of evidence for therapies currently utilised in the management of patients with POTS (Chapter 2). The results of our pilot study of CBFv in patients with POTS, and controls, is reported in Chapter 3. The contents of these 3 chapters have been published in peer reviewed journals.

In our pilot study, the effect of a visual stimulus on CBFv was measured using a handheld duplex TCD. We replicated the methodology previously used to demonstrate a reduction in neurovascular coupling (as demonstrated by a reduced CBFv response to a visual stimulus) in a study of patients with spinal cord injuries. (1) The rationale for replicating this methodology was the authors' attribution of the reduced neurovascular coupling in patients with spinal cord injury to disruption in the patients' autonomic feedback loops. As autonomic dysfunction has long been suspected to underlie the pathophysiology of POTS,(2) we considered the robust findings generated through the relatively simple methodology described by Phillips might prove useful in the study of patients with POTS. Unfortunately, this was not the case. Instead, we found similar changes in CBFv in our patient and control groups in response to the brief visual stimulus.

As a result of the negative findings from our pilot study (in which a brief visual stimulus was used), in subsequent studies we measured changes in CBFv during a prolonged cognitive stress. Not only was this stimulus a better reflection of the conditions during which patients typically experienced "brain fog" but it also allowed us to measure the effect of fatigue on symptoms scores, CBFv responses, and on cognitive performance.

As a result of difficulty in maintaining the angle of insonation in the posterior cerebral artery (PCA) over this prolonged cognitive stress (due to the small diameter of the PCA), we developed a protocol in which CBFv changes were measured in the middle cerebral artery (MCA). As a reduction in CBF may relate to hypocapnia in association with hyperventilation or increased tidal volume,(3),(4),(5) we included the measurement of respiratory rate and end tidal carbon dioxide (ETCO2) in studies with more prolonged stimuli.

The results of our study of CBFv responses to orthostatic and prolonged cognitive stress in POTS and control groups are reported in Chapter 4. In this study, we demonstrated that prolonged cognitive stress was associated with a greater reduction in CBFv in the MCA in the patient group when compared with controls. We also studied the effect of midodrine, an alpha adrenergic agonist, on CBFv in the MCA in patients with POTS undergoing orthostatic and prolonged cognitive stress. Participants in this study were selected based on their previous symptomatic improvement in response to midodrine. We set out to determine if this symptomatic response was associated with an improvement in CBFv response to prolonged cognitive stress. The results of this study (reported in Chapter 5) were inconclusive. Whilst patients reported a significant improvement in symptom severity, and we detected an improvement in reaction time during cognitive testing following midodrine, we did not demonstrate an improvement in hemodynamic or CBFv responses to cognitive or orthostatic stress following administration of midodrine. This negative study could reflect a placebo effect in reporting of symptomatic improvement or that the study was underpowered to demonstrate a difference in CBFv response, however it suggests that TCD measurement of CBFv in the MCA in response to orthostatic and prolonged cognitive stress may not be as useful as we had hoped as an objective marker of response for future therapeutic trials in patients with POTS.

In Chapter 6 we report on the use of plasma exchange therapy as a novel intervention in treatment resistant POTS. The use of plasma exchange in POTS was based on positive repsonses to plasma exchange in patients with a related condition (autoimmune autonomic ganglionopathy) (6) as well as reports of auto-antibodies in the sera of patients with POTS. (7)

The clinical course, cognitive and CBFv reponses to orthostatic and cognitive stress in a patient treated with acute and maintenance plasma exchange therapy are suggestive of some improvement with plasma exchange however the brief duration of response following each treatment and the lack of response in other patients did not support plasma exchange as a viable long term option for POTS.

Further studies are needed to evaluate TCD assessment of CBFv in POTS patients to define its utility in clinical practice. It would be of interest to study the CBFv response to prolonged cognitive stress after orthostatic stress in both POTS and control groups. A comparison of CBFv response to cognitive challenge measured by TCD with regional blood flow response using fMRI during an identical cognitive challenge would provide further insight into the utility of TCD as a tool to measure outcomes in clinical trials. As we advance our knowledge on the pathophysiology underlying this condition, a biomarker that correlates well with POTS symptom severity will be immensely valuable for clinicians managing this complex syndrome.

Thesis Publications

Wells R, Spurrier AJ, Linz D et al. Postural tachycardia syndrome: current perspectives. Vasc Health Risk Manag. 2018;14:1-11. (8)

Wells R, Elliott AD, Mahajan R et al. Efficacy of Therapies for Postural Tachycardia Syndrome: A Systematic Review and Meta-analysis. Mayo Clin Proc. 2018;93:1043-1053. (9)

Wells R, Hissaria P, Elliott AD et al. Plasma Exchange Therapy in Postural Tachycardia Syndrome: A Novel Long-Term Approach. Am J Med. 2019 (10)

Wells R, Patterson F, Bacchi S, et al. Brain Fog in Postural Tachycardia Syndrome: An Objective Cerebral Blood Flow and Neurocognitive Analysis. J Arrythmia 2020, DOI: 10.1002/joa3.12325 (11)

Chapter 1: Postural Tachycardia syndrome: current perspectives and literature review

Statement of Authorship for Postural Tachycardia syndrome: current perspectives

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Contextual statement

In addition to the published manuscript re-produced in this chapter (which provides an overview of POTS and its underlying pathophysiology), some additional detail is provided relevant to the contents of this thesis. Elaboration on the symptom of "brain fog" in POTS is followed by an overview of the use of TCD in the measurement of CBF dynamics and a description of the cognitive tools utilized in studies described in this thesis. Finally, the rationale for immunotherapy in patients with POTS is explored.

Introduction

Postural tachycardia syndrome (POTS) is a chronic debilitating condition characterized by symptoms of lightheadedness, fatigue, palpitations, pre-syncope, sleep disturbances, cognitive impairment and brain fog in conjunction with an exaggerated increase in heart rate (HR) when upright, despite maintenance of a normal blood pressure. {Garland et al., 2015, #90822} The exaggerated HR response is defined as a sustained increment >30 beats per minute (bpm) in adults, or >40 bpm in children, that occurs within 10 minutes of standing or head up tilt test (HUTT). The nonspecific nature of symptoms, bell curve of HR responses to orthostasis in the general population and a lack of specific biomarkers have made it difficult to establish the true prevalence of POTS but estimates put it at approximately 170 cases per 100,000 individuals in the general population. (13) The onset of POTS symptoms may be gradual although symptoms may also appear abruptly following an immunological stimulus, such as vaccination or an infective illness. (14) Cohorts of patients with POTS in association with symptoms of

head injury have also been described. (15) There is a higher than expected prevalence of joint hypermobility, irritable bowel syndrome (IBS) and chronic fatigue syndrome (CFS) in patients with POTS. (16) It is most commonly seen in adolescent and young adult females but can occur at all ages.

The pathophysiology underlying POTS may be multifactorial and vary in different subgroups. Autonomic dysfunction, dehydration, sympathetic tone, deconditioning, reduced venous return due to peripheral or splanchnic venous pooling may all contribute. (17) Autoimmunity and mast cell activation syndrome are thought to play a role in some patients with POTS. (7),(18),(19) Multiple system dysfunction and heterogeneity in presentation often lead to extensive investigation, with fragmented care provided by multiple specialists. In future, it may be possible to identify patients with genetic links, such as dysfunction of the noradrenaline transporter (NET), (20) which raises the possibility of targeted interventions such as the reactivation of NET. (21) However for the time being, therapies for this condition are limited and generally address intravascular volume, peripheral vascular tone or HR. Response to therapeutic interventions is variable and improvement in HR control does not always improve quality of life. (22),(23) Evidence base for POTS therapies is limited, with many options based on anecdotal evidence alone. (24)

The association between POTS and several other clinical syndromes is described below, followed by a discussion of our current approach to clinical history, physical examination and

targeted investigations to inform management. The potential to progress the evidence base for the clinical management of POTS is hampered by the heterogeneity of presentation and the lack of objectivity of symptom tools.

Concurrent clinical syndromes

Irritable Bowel Syndrome (IBS)

Symptoms of IBS, food intolerance and allergic sinusitis, are commonly reported in individuals with POTS. (13) Although rarely performed in clinical practice, studies utilizing plethysmography have demonstrated splanchnic venous pooling (consequent to localized small molecule related vasodilation) in patients with IBS. (25) An intact baroreflex response to the reduced venous return would explain the postural tachycardia seen in these patients. Nuclear medicine evidence of delayed gastric transit times may also reveal an autonomic neuropathy in some patients with concurrent IBS and POTS; however, an increased awareness of symptoms (hypervigilance) may be an important factor in others. (26) Serum tryptase taken immediately after an episode of flushing, or a 24-hour urinary N-methylhistamine level, may provide some evidence of mast cell activation; however, this is uncommon. (19)

Many patients go through a process of restricting their diet and/or food challenges for which standardized protocols may be used in an attempt to identify the triggers for symptoms of OI. (27) The benefit of a low fermentable oligo-, di- monosaccharides and polyoles diet is uncertain and a recent systematic review questioned the quality of evidence for this

approach.(28) Interestingly, the treatment of POTS may improve IBS symptoms, as seen in a cohort of children treated with fludrocortisone. (29)

Hypermobility Syndrome

Concurrent hypermobility, often referred to as Ehlers Danlos Syndrome, is overrepresented in patients with POTS. (30) The Beighton score is a standard tool used to document the presence of hypermobility. (31) Since hypermobility may reflect a connective tissue matrix weakness, a reduction in venous return due to poor vascular wall integrity, evident on ultrasound when the vessels collapse under gentle pressure from the ultrasound probe, can sometimes be observed. However, a higher prevalence of small fibre neuropathy in the hypermobile group and normal arterial stiffness (measured in large vessels using tonometry) suggest vessel wall integrity is not the only reason for concurrent joint hypermobility and POTS. (32) An association between anxiety, interoceptive sensibilities, chronic fatigue syndrome and either hypermobility or POTS has been reported by several groups. (33),(34),(35),(36)

Vascular Compression syndrome

Vascular compression syndromes such as median arcuate ligament syndrome, thoracic outlet syndrome and pelvic compression syndrome have the potential to reduce venous return and hence trigger the baroreflex to precipitate postural tachycardia. (37),(38),(39) Turbulent flow or high peak systolic velocities in the superior mesenteric arteries may be identified during Doppler ultrasound, especially when provocative maneuvers such as standing (Figure 1.1 A) and B), expiration or Valsalva increase the angle of the superior mesenteric arteries or celiac axis. (40),(41) Median arcuate ligament syndrome is an uncommon condition in which

patients develop postprandial or post-exertional abdominal pain secondary to intermittent obstruction of celiac or superior mesenteric arteries by the median arcuate ligament, sometimes in association with celiac plexus compression (Figure 1.1C). (42) Thoracic outlet syndrome describes the association of symptoms provoked by muscle, fascial or bony compression of vascular structures or nerve fibres at the thoracic outlet. Vessel flow characteristics during provocative maneuvers, such as elevation or abduction of the forearm, can be documented during ultrasound assessment (Figure 1.1D), although the false-positive rate can be significant. (43) Increased cardiac sympathetic activity might also be generated by compression of the stellate ganglion or postganglionic efferent sympathetic fibres. (37) While the peripheral and splanchnic vessels are most commonly implicated as the sites of venous pooling in POTS, pelvic vein varicosities may also result in significant venous pooling and can potentially be identified using transabdominal or transvaginal pelvic duplex ultrasound. Embolization or sclerotherapy can sometimes provide symptomatic relief. (44)

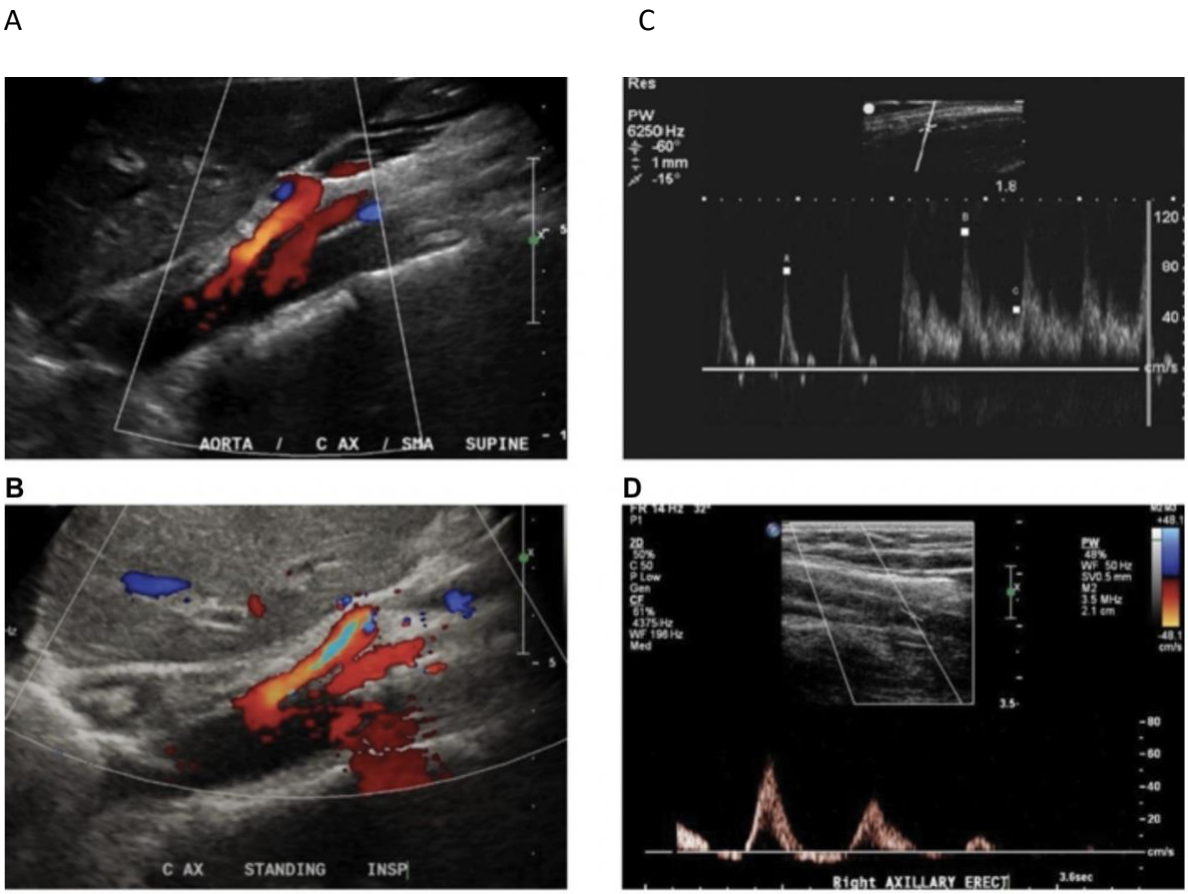

Figure 1.1: Pulse Wave Doppler ultrasound in vascular compression syndrome

Increase in Doppler intensity of the orange spectra and colour reversal due to aliasing (blue region in the centre of the vessel) indicates increase in blood flow velocity and turbulence in the compressed superior mesenteric artery of a patient upon change in posture from supine (A) to standing (B). In median arcuate ligament syndrome, the celiac artery may become compressed during expiration, resulting in increased blood flow velocity and turbulence, seen here as an increase in height during systole and broadening waveform during diastole (C). In thoracic outlet syndrome, the blood flow waveform is completely lost in the axillary artery upon arm raising (D).

Clinical approach toward POTS diagnosis

The range of complex nonspecific symptoms experienced by patients with POTS can impede management. Careful history taking and clinical examination are essential but exhaustive investigations often add little value to the overall management of this condition.

Clinical History

Individuals with POTS frequently present after a prolonged period of illness when OI may have developed as a result of deconditioning, disrupted circadian rhythm or dietary deficiencies. There is significant overlap in symptomatology between chronic fatigue syndrome (CFS), fibromyalgia, and POTS with no correlation between the severity of symptoms and the magnitude or consistency of postural tachycardia. Medical questionnaires can be useful in identifying relevant symptoms and past medical history sometimes lost in the plethora of symptoms offered by the patient. The circumstances surrounding symptom onset may suggest an autoimmune aetiology, with a traumatic or immunologic trigger. (14) Specific enquiry may also reveal concurrent conditions (Table 1.1) contributing to the severity of symptoms, including hypermobility, IBS or food intolerances, autonomic neuropathy and syncope.

Table 1.1: Concurrent and exclusion diagnoses in patients with POTS and orthostatic intolerance

Diagnosis	Relevant history	Relevant examination findings
Concurrent diagnoses in patients with POTS		
Syncope	Triggers and circumstances surrounding loss of consciousness episodes	No specific examination findings
Hypermobility	Recurrent subluxation or dislocation of joints, bruising tendency	Assessment of hyperextension at metacarpophalangeal joints, elbows, knees, hips and wrist flexion (Beighton score)
Irritable bowel syndrome	Frequent diarrhea, constipation and bloating	Abdominal tenderness and bloating
Autonomic neuropathy	COMPASS 31 questionnaire useful for an overview of autonomic symptoms (Table 1.2)	Lack of HR variability with deep breathing and significant postural hypotension
Postural hypotension	Orthostatic symptoms often resolve when recumbent, careful medication history	Lying and standing blood pressure with HR assessment
Exclusion diagnoses for patients with OI		
Anemia or iron deficiency	Blood loss (surgery, menorrhagia, melaena), reduced red meat consumption	Pallor, pale conjunctivae
Renal disease	Nausea, vomiting, fatigue, loss of appetite	Peripheral oedema, change in urinary pattern, treatment-resistant hypertension
Diabetes mellitus	Polydipsia, polyuria, fatigue	Ketotic breathe, unintentional weight loss
Diabetes insipidus	Polydipsia, polyuria	Signs of dehydration
Thyroid disease	Abnormal HR when recumbent	Resting tachycardia, eyelid retraction, goitre
Adrenal insufficiency	Prior steroid use	Skin pigmentation
Hypercorticolism	Steroid use	Striae, distribution of adipose tissue
Malignancy	Prior malignancy, weight loss, fatigue	Lymphadenopathy, breast lumps, palpable mass on rectal examination
Chronic infection	Febrile illness at the onset of symptoms	Fever
Pulmonary embolism	Chest pain, shortness of breath, recent immobility or previous deep vein thrombosis	Pleural rub, supine tachycardia, lower limb swelling
Arrythmias or cardiac disease	Palpitations, symptoms not exclusively related to posture	Abnormal pulse quality or rhythm, presence of cardiac murmurs

Specific enquiries on the use of supplements, current and previous medications can help identify the use of medications that may be exacerbating symptoms, either by reducing the intravascular volume (diuretics, mineralocorticoid receptor antagonists such as drosperidone), increasing vasodilation (calcium channel blockers, alpha-antagonists) or increasing fatigue (beta-receptor antagonists). Salt and water intake, sleep hygiene, physical activity capability and symptoms of anxiety and depression are important to elicit. The presence of concentrated urine despite good oral fluid intake suggests insensible fluid and electrolyte loss and may reflect exacerbation secondary to activities such as hot yoga. The timing and number of hours spent sleeping may identify significant abnormalities in circadian rhythm or other sleep disorders. POTS may sometimes be accompanied by cholinergic symptoms (decreased saliva and tear production, delayed gastric transit associated with early satiety, nausea, constipation and bladder dysfunction) (45) or associated with symptoms and signs of autoimmune conditions. (46) Several validated questionnaires may be useful to explore the presence of autonomic features and track severity of symptoms in patients with POTS (Table 1.2). (31),(47),(48),(49),(50)

Table 1.2: Adjunct Questionnaires

Questionnaire	Comments	Pros	Cons
COMPASS 31 (47)	Documents the presence of sudomotor, vasomotor, gastrointestinal, genitourinary, pupillomotor and orthostatic symptoms to reflect the extent of autonomic dysfunction	Provides an overview of symptoms related to autonomic function in terms of frequency and evolution	Presence of irritable bowel syndrome (which may not reflect autonomic dysfunction) can significantly affect the score
Winker (48)	Validated for occupational health assessments	Evaluates the frequency of 10 orthostatic-related symptoms	Does not provide a measure for symptom severity
Orthostatic Hypotension Questionnaire (49)	Validated in subjects with orthostatic hypotension and may be useful to evaluate acute changes during an orthostatic stress test	Likert scale recording the severity of six orthostatic symptoms (and ability to stand and walk for short or long periods)	Some uncertainties in scoring if symptoms ae severe but occur infrequently
Short Form 36 (SF -36) (50)	Widely used, well-validated scale for quality of life assessments	Contains 36 questions addressing social and functional domains reflecting the quality of life over the preceding 4 weeks	Some uncertainties in scoring if symptoms fluctuate or concurrent illness occurred during the 4 weeks
Beighton score (31)	One point for passive hyperextension of each elbow, each knee and each fifth metacarpophalangeal joint, as well as one point for hyperflexion of each wrist and one point for the ability to place the palms on the floor while standing with straight legs	Useful score for joint hypermobility	Does not discriminate between types of Ehlers Danlos Syndrome as there is no score for skin elasticity, bruising or genetic abnormalities

Clinical examination

HR and blood pressure (BP) should be assessed while the patient is supine and then during a 10-minute period of standing (Figure 1.2). If postural HR abnormalities are evident, tilt-table tests contribute little additional information. However, the timing and duration of the exaggerated HR response in patients with POTS has not been clearly defined, and the HR increment in an individual may demonstrate considerable daily variability. Therefore, if the patient reports typical postural symptoms but does not meet the criteria for POTS while standing in the clinic for 10 minutes, further investigation with tilt testing may still be warranted. (51) General physical examination may identify rashes, Raynaud's phenomenon or acrocyanosis of dependent limbs as a result of venous pooling (Figure 1.3 A and B). Auscultation for carotid, renal and epigastric bruits and cardiac murmurs should be undertaken along with examination of joints for evidence of hypermobility (Figure 1.3 C), and examination of pupillary reactions to detect evidence of cholinergic failure (Holmes–Adie pupil). Table 1.1 shows a list of conditions that may contribute to symptoms of OI in patients with POTS.

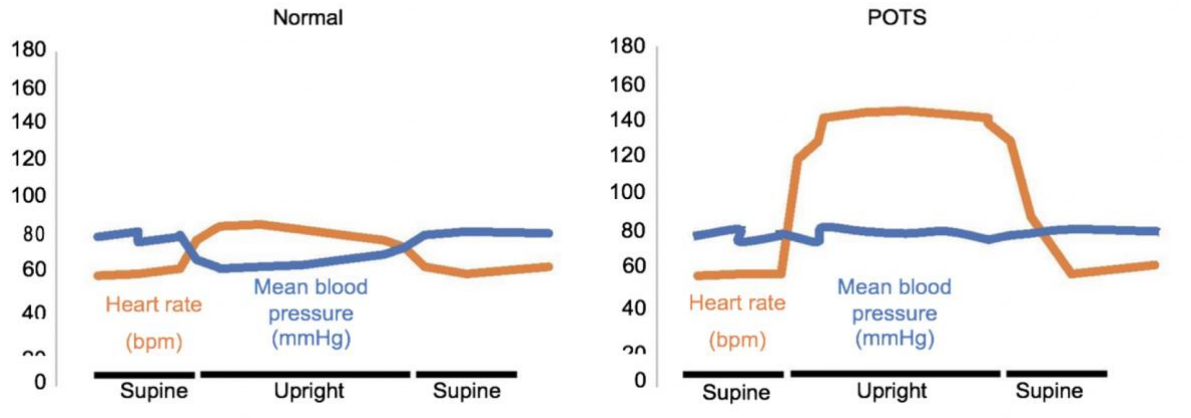

Figure 1.2 Supine and upright HR and blood pressure. Supine and upright HR (orange) and blood pressure (blue) profiles of a normal subject (left panel) and a subject with POTS (right panel) demonstrating an exaggerated HR increase > 30 bpm) and relatively stable blood pressure. Abbreviations: bpm, beats per minute; HR, heart rate; POTS, postural tachycardia syndrome

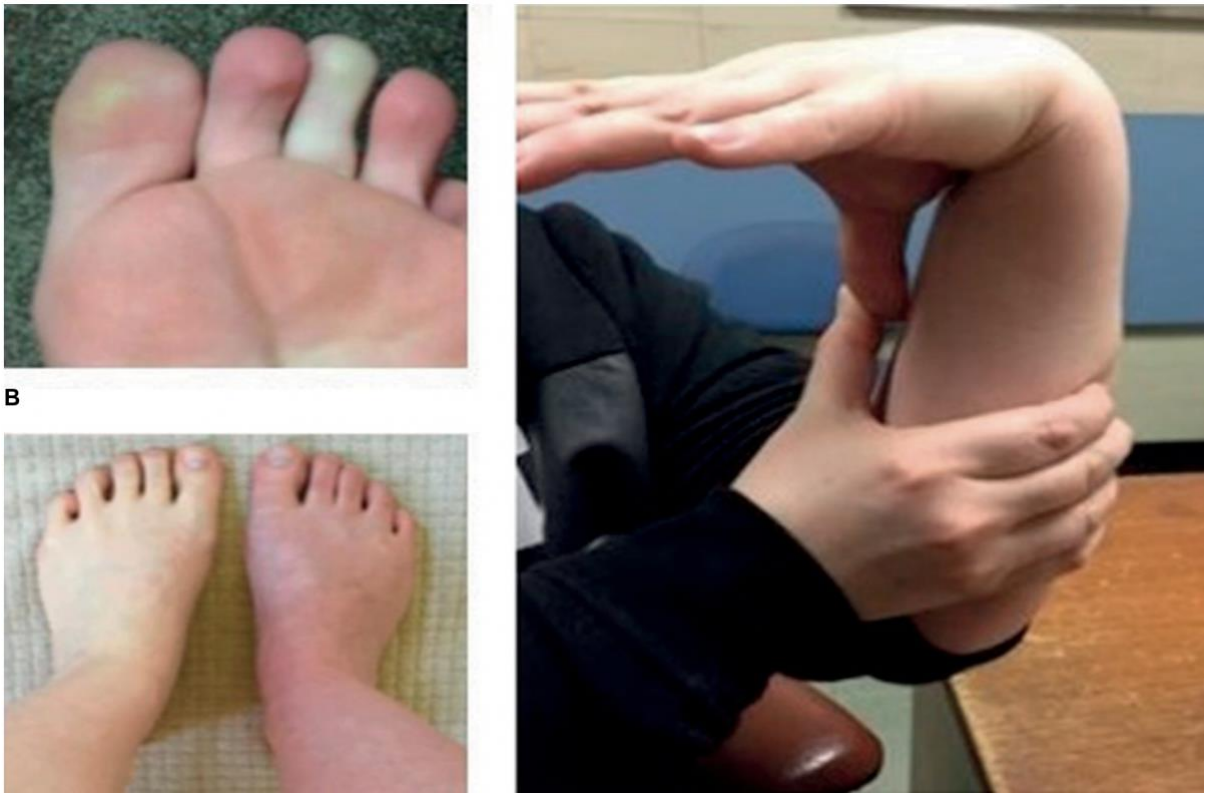

Figure 1.3. Common clinical signs. (A) Raynaud's phenomenon; (B) acrocyanosis; (C) hypermobility demonstrating the ability to bring the thumb in contact with the ipsilateral forearm as part of the Beighton score (for more information on Beighton scoring system, see Table 1.2). In (B), the right leg had been dependent whilst the left leg had remained on the bed for a few minutes revealing the colour change seen with venous pooling. Images were kindly provided by patients along with their written informed consent to publish the images

Investigations

Cardiovascular investigations

An electrocardiogram and 24-hour monitoring of cardiac rhythm may identify conduction abnormalities or unexpected arrhythmias on rare occasions. More commonly, sinus tachycardia is seen to correlate with symptoms of OI.

Tilt-table test

The head-up tilt-table test (HUTT) is the gold standard for diagnosis of orthostatic cardiovascular dysregulation and vasovagal syncope. HUTT increases the sensitivity to detect postural tachycardia as the calf muscles that contribute to venous return when standing are not engaged when the patient is supported on a tilt table. Some centers adopt a provocation protocol using either sublingual nitrates or intravenous infusion of isoproterenol. (52) Syncope can be induced in individuals without POTS or orthostatic dysregulation with sufficient provocation, however, and we do not recommend this approach. (53) While positive response to acute intervention with intravenous fluids and midodrine has been demonstrated during a 5-minute tilt test, this has yet to be correlated with long-term response. (54)

Autonomic Testing

Baroreceptors are stretch-sensitive mechanoreceptors located in the aortic arch and carotid sinuses. Changes in blood pressure alter the stretch of these mechanoreceptors, resulting in a rapid change in intensity of impulses in the autonomic nerve fibres projecting to centres in the brain. This in turn alters the intensity of impulses in the nerve fibres projecting from the autonomic centres of the brain to the sinus node, resulting in a rapid change in HR.

Elevated BP activates the baroreflex, leading to decreases in HR and BP. A drop in BP will inhibit the baroreflex, leading to increases in HR and BP. Baroreflex-induced changes in BP are mediated by both branches of the autonomic nervous system: the parasympathetic and sympathetic systems. Rapid baroreflex adjustments are critical for regulation of HR and peripheral vascular resistance during orthostatic stress. (55),(56) In individuals with reduced venous return during orthostasis but an intact baroreflex, persistent reduction in stretch of the baroreceptors results in an exaggerated and sustained tachycardia. During deep inspiration and expiration while supine, however, individuals with POTS generally have a normal variation in HR variability (preserved vagal function) as the baroreflex responds to changes in intrathoracic pressure. Immediately following a Valsalva maneuver, however, the normal rebound in blood pressure (phase IV) is exaggerated, reflecting a vigorous pressor response. A reduced ability to buffer a fall in activation (stretch) of the baroreceptors may occur in a subgroup of "hyperadrenergic" POTS patients with high background sympathetic tone.

Plasma and urine catecholamines

Hyperadrenergic POTS may relate to an increase in production of norepinephrine (57) or defective norepinephrine clearance. (58),(59),(60),(61),(62) The increment in norepinephrine after 10 minutes of head-up tilt versus supine rest has been used to dichotomize individuals with POTS into those with normal and those with hyperadrenergic responses. (63) Theoretically, patients with higher norepinephrine levels during HUTT are less likely to respond to alpha-agonist therapy (e.g., midodrine). One small study has shown patients with neuropathic POTS had a better HR response to midodrine when compared with patients with hyperadrenergic POTS, however symptomatic response was not evaluated. (64) A search

for single-nucleotide polymorphisms in the SLC6A2 gene encoding the norepinephrine transporter (NET) failed to demonstrate pathogenic variants in patients with POTS, (65) but the expression of NET on the cell membrane is dependent on phosphorylation and glycosylation, indicating that other genes or epigenetic modification may contribute to hyperadrenergic POTS. (66) Further, sympathetic denervation in neuropathic POTS could be expected to result in a decreased myocardial uptake of meta-iodobenzylguanidine, a noradrenaline analog readily taken up by sympathetic nerves via NET. (67) However, there was no correlation between cardiac meta-iodobenzylguanidine uptake and sympathetic skin responses, catecholamine levels, symptom severity or other autonomic parameters in POTS patients. (68) Measurement of norepinephrine and its metabolites are predominantly of interest as a research tool and are rarely performed in clinical practice to manage POTS.

Assessment of intravascular volume

Theoretically, low angiotensin levels may exacerbate POTS, as angiotensin has both a direct vasoconstrictor effect and drives renal fluid and sodium reuptake by stimulating aldosterone release from the adrenals. Lower than expected levels of renin and angiotensin were demonstrated in a group of patients with POTS, despite lower blood volume measures than the control group, although the implications of this finding for treatment are unclear. (69) Fludrocortisone, a synthetic aldosterone analog, is often used empirically to address the potential contribution of hypovolemia to orthostatic symptoms. In pediatric POTS patients with urinary sodium excretion <124 mmol/L per 24 hours, pretreatment symptom burden was significantly higher while posttreatment response to oral rehydration salts was significantly greater. (70) In practice, the assessment of intravascular volume, and integrity of the renin–

angiotensin system, are rarely performed, with techniques to measure total blood volume (carbon monoxide rebreathing, thermodilution, dye dilution, Technetium-99m or Chromium-51 labeled erythrocytes and Iodine-131 labeled albumin) typically reserved for research purposes only. (71),(72),(73)

Evidence of venous pooling can be demonstrated using labeled erythrocytes in conjunction with a gamma counter, impedance plethysmography and strain gauge measures of calf diameter increment during venous occlusion and head- up tilt. (74),(75),(76) Usually, individuals with POTS without excessive peripheral pooling have either hypovolemia (as demonstrated by indocyanine green dye dilution) or increased splanchnic blood flow despite peripheral vasoconstriction. (76) Using Doppler ultrasound, an increase in superior mesenteric artery blood flow can be demonstrated in some patients with POTS. (77) At present, the above tools are used primarily in research studies rather than to guide or assess response to therapy.

Immunologic workup

There is uncertainty around the significance of autoantibodies in POTS. (78) Sera from patients with POTS have produced exaggerated vascular constriction of a rat arteriole in vitro and an immunofluorescent assay identified autoantibodies binding to adrenergic receptors. (7) However, these tests are confined to research use and not used in current clinical practice. Autoantibodies targeting the components of nicotinic receptors are generally associated with orthostatic hypotension rather than tachycardia, but low levels of these, and many other

autoantibodies, have been detected in patients with POTS. (45),(79) At present, immunotherapy for POTS patients has been understudied and, in general, the risks are considered to outweigh the uncertain benefits. In contrast, immunotherapy has been successful in the treatment of generalized autonomic dysfunction associated with cholinergic autoantibodies such as in ganglionopathy. (80) Skin prick testing is sometimes undertaken to identify potential triggers to IgE-mediated mast cell histamine release. Urinary methylhistamine or serum tryptase levels performed on specimens taken during an episode of flushing and tachycardia may also provide some evidence of mast cell involvement. However, false-positive and -negative results may occur and ultimately, responses to food elimination diets and food challenges may provide the most clinically relevant information.

Brain Fog and Cerebral Blood Flow

Brain fog, most commonly described as “forgetful”, “difficulty thinking”, “difficulty focusing”, “cloudy” and “difficulty finding the right words or communicating” is a common symptom in POTS. (81) To determine the contribution of CBF dynamics to patient symptoms, Doppler ultrasound has been used to measure CBFv during postural maneuvers and cognitive tasks. (82),(83) Inability to buffer the cerebral circulation against peripheral circulation changes during orthostasis and excessive cerebral vascular constriction may be present, although these findings can be variable. (84),(85) An increased oscillatory pattern of CBF has been described in patients with POTS during head-up tilt that has been demonstrated to be associated with marked reduction in cognitive performance and functional hyperemia. (86),(82) Further, downregulation of nitric oxide receptor sites may explain the impaired nitric oxide-related cerebral vasodilation and blunted CBFv following administration of sodium

nitroprusside while supine and during upright tilt. (87)

End tidal carbon dioxide (ETCO2) is often used as a marker for the presence of hypocapnia, a cause of cerebral vasoconstriction which may contribute to cerebral hypoperfusion. (4),(88) A decrease in ETCO2 of 1mmHg decreases CBF by 3%. (4),(89) Hypocapnia may be the result of an increase in respiratory rate (hyperventilation) or an increase in tidal volume (hyperpnoea). (89) An increase in tidal volume has been demonstrated in a group of patients with POTS in whom the primary symptom was shortness of breath,(3) whilst hyperventilation was documented in a group of patients with POTS in whom excessive thoracic venous pooling during orthostasis was associated with an increase in sympathetic tone. (5)

Transcranial Doppler Ultrasound

The anatomy of the middle cerebral artery (MCA) is ideal for Transcranial doppler ultrasound (TCD) measurement of CBFv. The direction of blood flow is towards the temporal window (thinner area of bone above the zygomatic arch) through which the ultrasound beam can pass. The angle of the ultrasound beam relative to the flow through the vessel is termed the angle of insonance. To optimize the signal, this angle should be as close as possible to the direction of flow in the vessel and be maintained as stably as possible. In the MCA this is usually achievable with the signal identifiable over a range of depths (40-55 mm) in most individuals. CBF results obtained from TCD assessment of CBFv in MCA correlate well with gold standard methodology for quantifying CBF. (90)

Transcranial doppler ultrasound (TCD) provides an output of mean CBFv, taking into account the range of velocities (due to the laminar flow) in the vessel. (91) Outcome measures obtained from duplex ultrasound of the CBFv waveform include mean velocity (MV) often expressed as time averaged peak (TAP), peak systolic velocity (PSV), end diastolic velocity (EDV), as well as calculated indices of resistance index (RI) and pulsatility index (PI), where PI = (PSV – EDV) / MV. (92) PI is high when cerebral vasoconstriction or high intracranial pressure results in decreased diastolic flow.

Non-duplex TCD is a convenient, non-invasive technique that allows for real time recording of the CBFv waveform. Duplex, or Transcranial color-coded duplex ultrasonography (TCDD) provides the capability to directly visualise the insonated artery. (93) The imaging modality can be helpful in locating the posterior cerebral artery (PCA), a smaller diameter vessel with direction of flow at an obtuse angle relative to an ultrasound beam directed through the temporal window. Near infrared spectroscopy may provide an alternative to TCD CBFv in studies of cerebral hypoperfusion but is less sensitive to regional CBF changes when compared with TCD. (94)

Usually, dynamic autoregulation ensures CBF is maintained despite spontaneous changes in BP secondary to standing, exercising or respiratory related alterations in venous return to the heart. (95) Symptoms of hypoperfusion become noticeable when CBFv is reduced by 50%. (96) Since BP is, by definition, maintained in patients with POTS,(97) and POTS children and young adults have previously been found to have intact autoregulation,(98) the cognitive difficulties encountered by patients with POTS may relate to impaired

neurovascular coupling (NVC). NVC is the increase in regional CBF in response to increased metabolic demands. (99),(100)

Cognitive assessment

A standardised cognitive stress, in association with measures of CBF, allows for simultaneous assessment of neurovascular coupling and cognitive performance. Cambridge Neuropsychological Test Automated Battery, (CANTAB) (Cambridge Cognition Ltd., Cambridge, UK) is an ipad based neurocognitive assessment program in which tasks are accompanied by recorded instruction scripts, reducing the potential for unconscious bias introduced by individuals administering the neurocognitive tasks. (101) Others have reported good test / re-test reliability with CANTAB tasks. (102) CANTAB includes tasks designed to assess function in different cognitive domains including attention and psychomotor speed, memory, and executive function (Table 1.3). Multiple output variables are recorded for all tasks.

Table 1.3: CANTAB cognitive domain tasks

Task	Cognitive domain	Outcomes used in our studies
RTI RVIP	Attention and psychomotor speed	RTI: reaction time RVIP: correct responses
DMS	Memory	DMS: correct responses for trials with 12 second delay
MTT (AST)	Executive function	MTT: correct responses

RTI: reaction time index, RVIP: rapid visual information processing, DMS: delayed matching to sample, PAL: paired associates learning, SWM: spatial working memory, MTT: multi-task (previously referred to as AST: Attention switching task)

Reaction time index (RTI) and Rapid visual information processing (RVIP) provide multiple trials within each task, increasing the potential to capture subtle changes in cognitive ability in the domain of attention and psychomotor speed. A pre-recorded script for the Reaction time index (RTI) task directs the participant to release a button and tap a target when it appears on an ipad screen. This simple task allows participants to become familiar with listening to recorded instructions and to respond by touching the ipad screen whilst assessing motor response time. The Rapid visual information processing (RVIP) task is more challenging and requires sustained attention. During this task digits appear on the screen (at a rate of 100 digits per minute) and participants are directed to press a button whenever they identify any of the three target sequences (2-4-6, 3-5-7, or 4-6-8). The brief time between appearance of digits minimises the risk of conscious or unconscious manipulation of results. The high number of target sequences to identify provides the opportunity to discriminate between relatively subtle levels of cognitive dysfunction. (103)

In the Delayed Match to Sample (DMS) task, participants are shown a complex multicoloured, geometric object. A training phase of the task keeps the target object in view while the participant identifies the matching object from 4 options provided below the target object. In the assessed trials, the target object disappears for 4, 8 or 12 seconds before the response options appear. The multitasking test (previously referred to as the attention switching task (AST) provides an assessment of executive function. In this task participants touch “left” or “right” buttons in response to a single word question, “direction” or “side” appearing at the top of the screen. The target image to which the question refers is an arrow that appears in different orientations and positions on the screen.

Approach to therapy for patients with POTS

The first consideration in managing POTS is patient education concerning pathophysiology and symptoms, with numerous simple lifestyle strategies aimed to reduce the burden of POTS-related symptoms. Table 1.4 provides a summary of the approach to treating POTS patients based on their dominant symptoms.

Table 1.4: Choice of therapy based on phenotype

Symptoms or signs	Rationale	Therapy
All patients	Avoidance of external factors contributing to orthostatic-related symptoms	Avoid overheating, elevate head of bed, lifestyle management including diet, sleep hygiene and a recumbent exercise program(104) Use of physical counter maneuvers and tonic muscle contraction to combat pre-syncopal symptoms
White/cold peripheries and narrow upright pulse pressure (systolic-diastolic BP)	Suggestive of low blood volume	Increase oral salt and water intake and consider adding fludrocortisone
Acrocyanosis of dependent peripheries	Possible venous pooling	Use of compression garments when upright(74) and consider adding vasopressor therapy (e.g., midodrine)
Supine heart rate >90/minute	Increased circulating noradrenaline	Confirm normal thyroid function tests, anxiety management, rate control with low dose beta2 antagonists (propranolol) or ivabradine
Concurrent IBS	Splanchnic pooling	Consider referral to a dietician and/or trial of an elimination diet

Non-Pharmacological interventions

Receiving an explanation for the physiologic basis underlying POTS can be very reassuring for patients. Furthermore, strategies to avoid triggers and manage symptoms are more likely to be adopted if patients understand the underlying rationale. Nonpharmacologic strategies include avoidance of exposures that may contribute to overheating, improving venous return by activation of calf muscles and tonic muscle contraction when lightheaded. Maintaining good hydration may include supplementing salt and water intake and withdrawal of medications that interfere with fluid balance (drospirenone, diuretics). Where food intolerances are problematic with suspected splanchnic pooling, providing dietary advice and referral to a dietician may be of benefit. The use of full-length pressure stockings can be of considerable benefit in reducing POTS symptoms. Previously, it has been demonstrated that a 45–50 mmHg inflatable pressure suit significantly reduced abnormal HR and blood pressure responses when patients with orthostatic intolerance were upright. (74) However, difficulty in applying compression garments and reduced user compliance during warmer weather (when they are likely to be of greatest benefit) limit the translation of potential benefits from external compression into significant benefit in many patients.

In patients with autonomic failure, sleeping in a seated position can reduce loss of salt and water at night. (105) It has been postulated that increased renin secretion and consequent aldosterone increase can occur with reduced renal arterial pressure when a patient lies with the head of the bed raised by ~10 cm. Further, a graduated exercise program incorporating recumbent exercises may also be beneficial in POTS. (104) Short-term exercise training has

been shown to increase the baroreflex sensitivity in POTS patients and decrease the upright HR. (106) It is important to keep a modest expectation of activity levels in the early phase to avoid post-exertional fatigue and abandonment of the program, as a gradual increase in exercise can result in significant improvement in both symptoms and orthostatic HR in patients with POTS. (104),(107),(108) Other lifestyle factors include adoption of good sleep hygiene to address disrupted circadian rhythm, and psychologic support, to encourage realistic expectations of integration back into the study or workplace.

Pharmacological interventions

A recent consensus statement has highlighted a lack of quality evidence for the use of pharmacotherapy in POTS. (109) Empirical trials of medications are generally adopted based on the clinician's impression of the POTS phenotype (Table 1.3). In practice, single or combination therapies directed at increasing intravascular volume, increasing peripheral vasoconstriction and controlling HR are often employed. Fludrocortisone is a reasonable option for increasing the intravascular volume, while midodrine is useful in those with peripheral pooling.

Specifically, midodrine was superior to placebo in the subgroup of patients with peripheral venous pooling (as indicated by an increase in calf diameter during venous occlusion or tilt), whereas in patients without peripheral pooling, the HR change with midodrine was not significantly different from placebo. (64) Nonselective beta2 antagonists such as low-dose propranolol may be effective for treating the elevated HR. (110) These are preferred over the cardio-selective ones, given the added potential for reducing pathogenic peripheral or

splanchnic vasodilation. One major limiting factor in the use of a beta2-receptor antagonist is the potential for worsening chronic fatigue symptoms that are often present in POTS patients. Ivabradine is an alternative rate control agent with some benefit in POTS. (111) Rescue therapy with intravenous saline during acute decompensation can be helpful, and intermittent infusions can sometimes be considered in highly symptomatic patients in whom standard therapy has failed. (112)

Miscellaneous interventions

Several other POTS interventions have been reported in case series. In specialized centers, patients with significant postprandial tachycardia are occasionally treated with octreotide, a somatostatin analog, used to reduce splanchnic pooling. (113),(114) However, the need for subcutaneous or intramuscular administration, as well as the cost and side effect profile of octreotide have limited its use. A small case series on sinus node modification has found no significant benefits. (115) There is minimal information on the effect of immunomodulatory therapies, despite data suggesting a correlation between immune dysregulation and POTS. (116) Good response to intravenous immunoglobulin has been described in two patients with POTS in association with antiphospholipid syndrome. (117) Several miscellaneous therapies have been reported in POTS patients, but these remain investigational: erythropoietin, modafinil, methylphenidate and pyridostigmine. (118),(119),(120),(121) The predominance of POTS in young females could reflect an interaction between female hormones and mineralocorticoid receptors; however, the effect of manipulating female hormones requires further study. Oral contraceptives containing drosperinone are theoretically best avoided, given they are antagonists at the

mineralocorticoid receptors. (122) A trial of histamine antagonists may also be considered where vasodilation secondary to histamine release appears to be a contributing factor.

Prognosis

While there is no evidence for increased mortality associated with POTS, significant morbidities may persist. The prognosis of this condition is difficult to ascertain due to the heterogeneity and our incomplete understanding of the underlying pathology. Nevertheless, insights on the prognosis can be gained from the reports from several centers. A prospective, longitudinal study of 56 patients who were treated at the Mayo clinic with a combination of nonpharmacologic interventions and beta-blockers (54%), fludrocortisone (24%) or midodrine (17%) found improvement in 70% of patients, while 30% became worse after 1 year of treatment. (123) A retrospective review of POTS patients from the same clinic showed symptomatic improvement in up to 80%, although only 33% were managing recreational activities 5 years after diagnosis and 73% were still requiring treatments. (124) Questionnaires returned by 172 of 502 patients from another retrospective study indicated symptom resolution in 19%, improvement in 51% and unchanged or worsened symptoms in 12% of POTS patients at 5 years. (125) Thirty-one percent of patients responding to a phone questionnaire reported being asymptomatic ~10 years after their first consult. (126) Taken together, the majority of POTS patients may experience improvements in their symptom severity, while symptom progression and complete recovery are evident only in a minority.

Future prospects – immunotherapy

It has been known for decades that the autonomic and immune systems are intimately connected. The “inflammatory reflex” or “cholinergic anti-inflammatory pathway”(127) is triggered by inflammatory cytokines released in response to an infection or inflammation binding to receptors on afferent vagal fibres. Connections in the midbrain result in down-regulation of sympathetic outflow, activation of the hypothalamic-pituitary axis and activation of the vagal dorsal motor nucleus in the medulla from which efferent vagal fibres carry the signal throughout the body, resulting in the production of anti-inflammatory cytokines. (128) Since vagal tone is also controlled through baroreceptor stimulation, and sympathetic activity is modified by anxiety and physical activity, it is not surprising that autonomic function is altered in patients with immune dysregulation and patients with autonomic dysfunction may have altered immune regulation.

Invitro experiments have demonstrated that sera and IgG fractions from patients with POTS affect animal arterioles and heart myocytes, altering constriction and rate of contraction respectively through interaction with adrenergic, muscarinic and/or nicotinic receptors.(7),(129) Through comparison of control and patient IgG and confirmation with mass spectroscopy and immunoblot against commercial antibodies, Wang et al were able to demonstrate the sera from patients with POTS contained 70 unique autoantibodies against proteins in cardiac lipid rafts. (79) (Lipid rafts are platforms within plasma membranes important in the integration of signal transduction.) The antibodies bound proteins specific to multiple cell functions including energy and adrenergic pathways. Thus, it appears that multiple autoantibodies may contribute to the clinical syndrome of excessive tachycardia in

response to orthostatic challenge in at least a subset of patients with POTS.

The risk of many immunotherapies outweighs the potential for benefit in a non-lethal condition such as POTS. Plasmapheresis has a low risk profile, however, and is used routinely in the collection of immunoglobulin from healthy donors, often on a weekly basis. (130) During plasmapheresis, cells are separated from plasma and returned to the patient. The plasma is either filtered, extracting antibodies before returning to the patient, or it can be discarded and the patient is given fluid replacement, usually with 4% albumin (plasma exchange). Plasmapheresis is used for acute treatment of a number of conditions in which autoantibodies are pathogenic (Guillain Barre Syndrome, Myasthenia Gravis, Chronic Idiopathic Demyelinating Polyneuropathy), primarily to treat a patient during an acute flare of disease, since it does not prevent further antibody production.

Reports of the use of plasmapheresis as a therapy in patients with orthostatic intolerance are limited. A case series of 6 patients with a phenotype of autoimmune autonomic ganglionopathy (AAG) noted improvement following immunotherapy tailored to the individual response (intravenous immunoglobulin, progressing to plasmapheresis +/- mycophenolate mofetil). (80) In a series of 3 patients with AAG, treatment with plasmapheresis was followed by an improvement in cognitive function but no change in hemodynamics whilst seated. (131)

The effect of plasmapheresis in patients with POTS is unknown. If autoantibodies are driving orthostatic tachycardia, however, removal of these autoantibodies by plasma

exchange may reduce morbidity in POTS patients resistant to other therapies. Plasma exchange places a significant burden on limited medical resources, however. Thus, validation of objective measures of response to the use of plasma exchange is vital. Since HR control has not correlated with symptom severity in previous studies of POTS, objective measures of cognitive function and CBF are potential parameters to guide treatment selection and assess clinical response in future clinical trials for POTS.

Conclusion

The mechanisms underlying POTS are complex and remain poorly understood. The diagnosis is based on clinical history and determination of BP and HR responses in the upright posture. Targeted investigations focusing on autonomic function, assessment of intravascular volume, genetic and immunologic workup may help to identify factors contributing to the symptom complex in a subset of patients. Currently, therapies for this condition focus on symptom control but in future the potential for therapies targeting genetic or immunological anomalies may be considered. Further research is needed to help clarify the optimal approach to diagnosis, evaluate novel therapeutics, and inform long-term prognosis of this debilitating condition. The subjective nature of symptom questionnaires and the limitations in cognitive assessment tools to detect small changes in cognitive function call for more objective physiologic measurements that can be used to guide clinical management of this debilitating condition.

Chapter 2: Efficacy of Therapies for Postural Tachycardia Syndrome: A Systematic Review and Meta-analysis

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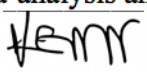

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Contextual statement

In this chapter, the paucity of evidence for therapeutic interventions currently considered standard of care is detailed. One of the major difficulties in performing randomised controlled trials in POTS is the lack of objective outcome measures. Symptom scores are therefore the usual measure of "efficacy" in these studies and thus the tools utilised to assess symptom scores are discussed. Detail on the level of symptom score considered to represent efficacy is often missing, however. Key areas for future research in this condition is therefore the standardisation of symptom assessment and the correlation of symptom score with an objective biological marker.

Abstract

Objective: To identify the evidence base and evaluate the efficacy of each treatment for postural tachycardia syndrome (POTS) in light of a recent consensus statement highlighting the lack of treatment options with clear benefit to risk ratio for this debilitating condition.

Patients and Methods: The CENTRAL (Cochrane Central Register of Controlled Trials), Pubmed and EMBASE databases from inception to May 2017 were searched using the terms "postural" AND "tachycardia" AND "syndrome". A total of 135 full-text publications were screened after excluding duplicates (n=681), conference abstracts (n=467) and records that did not relate to POTS therapy (n=876). We included 28 studies with at least 4 POTS patients in which symptomatic response was reported after more than 4 weeks of therapy. This review was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. Two investigators independently performed the data extraction and evaluated the quality of evidence.

Results: This study comprised a total of 25 case series and 3 small randomized controlled trials that evaluated 755 and 103 patients with POTS, respectively. Interventions directed at

increasing intravascular volume, increasing peripheral or splanchnic vascular tone, controlling heart rate and increasing exercise tolerance demonstrate moderate efficacy (range 51-72%). Few data exist on their comparative effectiveness. Significant heterogeneities were seen in terms of patient age, symptom severity, and the measures used to evaluate treatment efficacy.

Conclusion: The current evidence base to guide optimal management of patients with POTS is extremely limited. More high-quality collaborative research with standardized reporting of symptom response and treatment tolerability is urgently needed.

Introduction

Postural tachycardia syndrome (POTS) is a chronic debilitating condition that can substantially affect quality of life (QOL), cognition and psychosocial well-being. (8),(26),(132),(133) Its prevalence has been estimated to be 170 cases per 100,000 individuals. (134) The hallmark of POTS is a sustained heart rate increment of more than 30 beats per minute (bpm) in adults (>40 bpm in children aged 12-19 years) during the first 10 minutes of head up tilt (or upright posture) in association with symptoms of orthostatic intolerance (e.g. pre-syncope, brain fog) and in the absence of orthostatic hypotension. (97),(135) Usually, the symptoms of POTS develop in childhood or early adult life and is seen predominantly in females. (97) Patients with POTS commonly report symptoms of palpitations, dizziness and visual disturbances that often improve when recumbent. Symptoms of fatigue and difficulties with cognition are often less responsive to postural manoeuvres. Two main subtypes of POTS have been described, with neuropathic POTS involving reduced noradrenergic vasoconstriction in the extremities or the splanchnic vasculature, and hyperadrenergic POTS

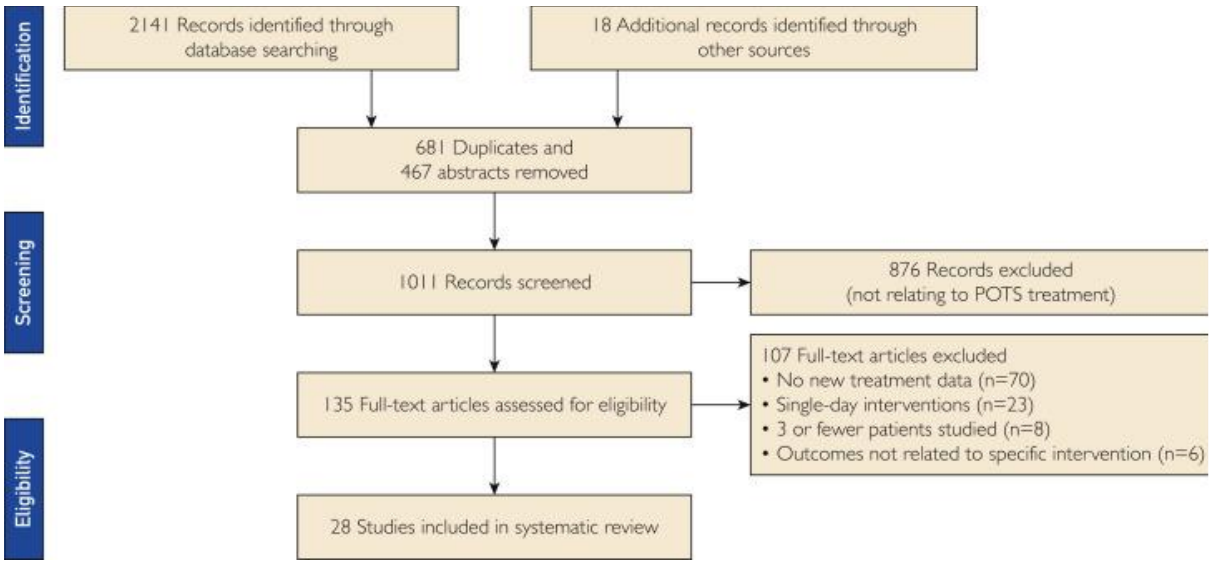
involving excessive noradrenergic vasoconstriction, reduced calf blood flow, and prominent symptoms of sympathetic activation. (64),(132),(134)

Recently, the Heart Rhythm Society released an expert consensus statement on the diagnosis and treatment of POTS. (109) Strikingly, there was a lack of randomized controlled trial (RCT) data on POTS treatment, with most recommendations derived from consensus opinions or weaker studies. Furthermore, there was a distinct lack of management strategies with clear benefit to risk ratios for this condition (Class IIa or higher according to the American College of Cardiology Foundation/American Heart Association Taskforce on practice guidelines). We therefore undertook a thorough systematic review and meta-analysis of the literature to clarify the current evidence base surrounding the treatment of POTS and evaluate the efficacy of the different options to guide further research directions.

Methods

A search of the CENTRAL (Cochrane Central Register of Controlled Trials), PubMed and EMBASE databases from inception to May 2017 using the terms “postural” AND “tachycardia” AND “syndrome” extracted 2,141 records (Figure 2.1). A further 18 records were identified from references of review articles. We then excluded duplicates (n=681), conference abstracts (n=467) and records that did not relate to treatment of POTS (n=876). The full text of the remaining 135 articles was reviewed to identify original data regarding a symptomatic response to any specific therapy over at least 4 weeks.

Figure 2.1. Selection of studies



The Heyland Methodological Quality Score was used to rate the quality of the RCTs. The score does not take into account the power of the study to identify a true difference between groups, but it does take into account patient selection, degree of blinding to intervention, whether groups were equal at baseline, whether co-interventions were adequately described and equal across groups, whether objective definitions of outcome measurements were used, and whether all patients were properly accounted for in the analysis (intention-to-treat). Case series were given a rating of 4 using the quality rating scheme modified from Oxford Centre for Evidence-Based Medicine. Each of the included studies was assessed independently by 2 investigators (RW and DHL). Discordant assessments were resolved by discussion. For each study, the following data elements were extracted: patient number, mean age and percentage of females in the study, study design, intervention

(including dose, mode and frequency of administration), duration of follow-up, symptomatic efficacy and the tool used to measure symptomatic response. Treatment efficacy was often reported after excluding patients discontinuing therapy or lost to follow-up. We therefore extracted the number of individuals in all arms of each study and, where available, the number of individuals excluded from the intention-to-treat cohort during efficacy calculations.

We performed a meta-analysis of individual study data showing treatment efficacy when there were at least 2 studies evaluating the same therapy. Efficacy, defined as proportion of the responders in each study cohort, was transformed using the Freeman-Tukey arcsine transformation and was pooled across studies using the DerSimonian-Laird random effects method. Pooled estimates and their 95% CIs were back-transformed to give summary percentages for each treatment. Statistical heterogeneity was assessed using the I^2 statistic.

Publication bias was assessed by visual inspection of funnel plots and statistical assessment of asymmetry based on a weighted linear regression of treatment effect on standard error where sufficient data were present (>6 studies). All data were analyzed using R software version 3.3.0.

Results

Study selection

Of the 135 full text publications reviewed, 70 were excluded as no new treatment data was reported (Figure 2.1). Thirty-seven publications were further excluded for the following reasons: 8 reports involved 3 or fewer patients; 6 did not relate outcomes to a specific

intervention, and 23 involved single-day interventions without longer-term follow-up data. Thus, the final analysis included 28 publications reporting symptomatic outcomes after treatment of 858 patients with POTS. Both pediatric and adult patients were included because onset of POTS is common from childhood to early adult life.

Intravascular volume expansion

There were 5 publications involving 160 patients treated with strategies directed toward increasing intravascular volume (Table 1). (23),(29),(112),(136),(137) The efficacy for intravascular volume expansion reported in these publications ranged from 53% to 93%. Notably, patient populations were heterogeneous, with predominantly treatment-naïve pediatric patients with mild symptoms in the studies of oral supplements and predominantly treatment-resistant adult patients in the studies of intravenous (IV) fluid supplementation. Only 1 of these studies included randomization to alternate treatment strategies. This RCT consisted of a control arm of 15 children (aged 6-17 years) given advice to increase salt and water intake. Children in the other 2 arms of the study were given either midodrine or beta-receptor blockers. (23) The remainder of the intravascular volume publications are case series describing outcomes after oral rehydration solution, intermittent IV fluid infusion, or oral fludrocortisone. Ruzieh et al. (112) describe a 93% efficacy with long-term IV fluid administration in treatment-resistant patients. The publication by Fortunato (29) involved a small group of children with POTS presenting with gastrointestinal symptoms. (29) Assessment of efficacy in this study was based on the individual symptoms that improved (nausea, dizziness, abdominal pain, flushing, and missing school improved, but scores for vomiting, syncope, constipation, and anorexia did not) rather than on the number of patients

responding. A commonly cited publication including patients with orthostatic intolerance was not included because it is unclear whether these patients had POTS. We did not find publications matching the search criteria that related to the use of desmopressin.

Legend Table 2.1: Intravascular volume expansion & Vasopressor

[a]bid = twice daily; CNHSQ = Children's National Health System Questionnaire (25 questions assessing quality of life); IM = intramuscular; LAR = long acting release, NA= not available; OHQ = Orthostatic Hypotension Questionnaire; RCT = randomized controlled trial; SC = subcutaneous; SQ (28) = 28 symptom questionnaire; WFDI = Walker Functional Disability Inventory; WSS = Winker symptom score; tid = three times daily;

[b]Heyland Methodological Quality Score of 8 or greater denotes high quality; all other studies graded 4 using the rating scheme modified from the Oxford Centre for Evidence-Based Medicine represent case-series or case-controlled studies;

[c]Includes patients with orthostatic hypotension;

[d]Unclear if 79% of patients improved or if mean improvement in symptoms across the whole cohort (including patients with hypotension) was 79%;

[e]Includes patients with syncope;

[f]Results reported by symptom, not by patient;

[g]Symptomatic response in patients with postural tachycardia syndrome was not reported separately.

Table 2.1: Intravascular volume expansion & Vasopressor

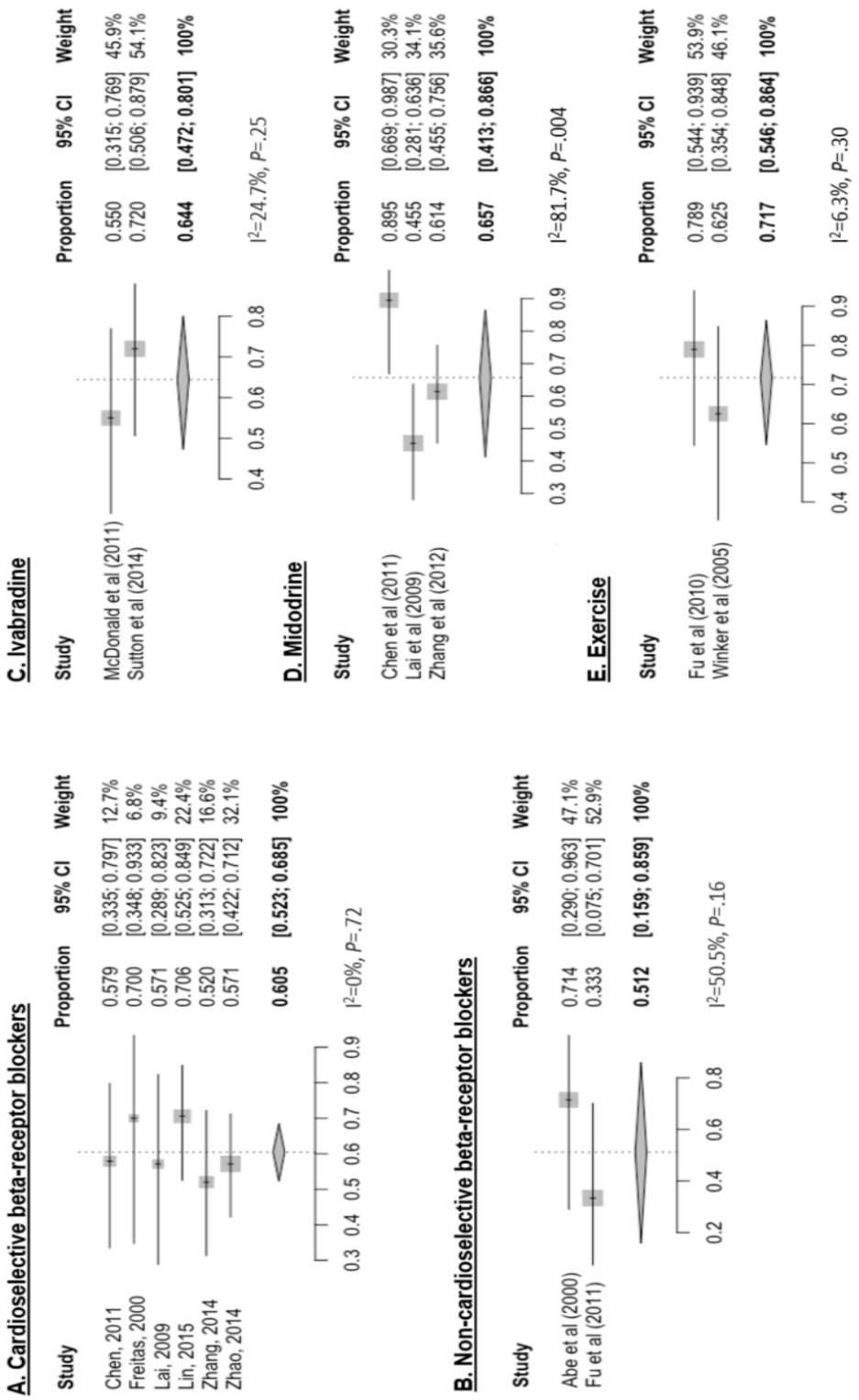
Reference, Year	Total patients in study (No.)	Patients included in efficacy calculation (No.)	Patients excluded from efficacy calculation (No.)	Age (y) mean	Female (%)	Treatment	Trial design	Symptom tool	Efficacy (%)	Follow-up (d)	Evidence grade/ quality
Oral Salt/Water											
Chen et al,(23) 2011	53	15	0	12	58	Salt + water	RCT	WSS	53	168	8[b]
Li et al,(136) 2016	110	54	0	12	41	Oral rehydration solution	Case series	9 symptoms	54	90	4
Intravenous saline											
Moak et al,(137) 2016	39[c]	24	Unknown	16	82	1-2L, 3-5x/wk	Case series	CNHSQ	79[d]	203	4
Ruzieh et al,(112) 2016	72	57	15	35	97	1-2L, 1-4 weekly	Case series	OHQ and SF-36	93	>90	4
Fludrocortisone											
Fortunato et al,(29) 2014	16[e]	10	0	14	100	0.1-0.2 mg/d	Case series	10 symptoms	NA[f]	28	4
		160		18					70		
Midodrine											
Chen et al,(23) 2011	53	19	0	12	58	2.5 mg/d	RCT	WSS	89	147	8[b]
Lai et al,(138) 2009	121	13	Unknown	14	77	NA	Case series	WFDI	46	NA	4
Zhang et al,(139) 2012	77	44	13	11	NA	2.5 mg/d	Case series	WSS	61	90	4
		76		12					65		
Droxidopa											
Ruzieh et al,(140) 2016	352	37	17	48	76	100-600 mg tid	Case series	None	27	NA	4
Octreotide											
Hoeldtke et al,(141) 2007	11	4	0	35	100	LAR IM 10-30mg fortnightly	Case series	SQ (28)	NA[g]	90	4
Kanjwal et al,(113) 2012	12	5	0	33	NA	50-100 mcg bid-tid SC	Case series	None	NA[g]	69	4
Subtotals		**9**		**34**					**NA**		

Vasopressor therapy

Six studies reported on the symptomatic outcomes following vasopressor therapy (Table 2.1). The vasopressor agents included midodrine (3 publications, 76 children),(23),(138),(139) droxidopa (1 publication, 37 patients),(140) and octreotide (2 publications, 9 patients). (113),(141) Midodrine was superior to conventional therapy (salt supplementation) in the nonblinded RCT involving pediatric patients, despite the very low dose being used. (23) The data from Lai et al (138) relate to a postal survey in which adolescents were asked which medications had improved their symptoms.

The pooled efficacy for midodrine in these pediatric studies was 66% (95% CI 41-87%) (Figure 2.2), with evidence of statistical heterogeneity across studies (I^2=81.7%, P=.004). Comparable data on the symptomatic response to midodrine in adults that meet the review criteria was lacking. The poor efficacy of droxidopa was based on a retrospective review of a single center's experience and was unsurprising given that most of these patients had previously failed to respond to other vasopressors. (140) Of the 40 patients known to have commenced droxidopa, only 10 patients reported improvements at the time of the review. Octreotide was also utilized in treatment-resistant patients. The exact efficacy was difficult to ascertain (between 50-100%) due to combined reporting of outcomes for all patients with orthostatic intolerance, including patients without POTS. (113),(141)

Figure 2.2: Meta-analysis of studies of the individual therapeutic modalities beta-receptor blockers, ivabradine, midodrine, and exercise. Proportion of responders to: (A) Cardioselective beta-receptor blockers; (B) Non- cardioselective beta-receptor blockers; (C) Ivabradine; (D) Midodrine and (E) Exercise



Heart rate reduction

There were 10 publications describing symptomatic response over at least 4 weeks after interventions directed toward rate control (Table 2.2). The rate control agents included cardioselective beta-receptor blockers (1 small RCT, 5 case series, 151 patients),(23),(138),(142),(143),(144),(145) non-cardioselective beta-receptor blockers (1 small RCT and 1 case series, 16 patients), (22),(146) and ivabradine (2 case series, 45 patients). (111),(147) None of the studies reported on treatment efficacy in patients with hyperadrenergic POTS specifically. The pooled efficacy was 60% (95% CI, 52%-69%; I^2=0%, P=.72) for cardioselective beta-receptor blockers (Figure 2.2 [A]) and 51% (95% CI, 16%-86%; I^2=50.5%, P=.16) for noncardioselective beta-receptor blockers (Figure 2.2 [B]). There was no evidence of publication bias amongst studies reporting efficacy of cardioselective beta-receptor blockade (P=.64). Notably, there was no statistically significant difference between the symptomatic response in patients receiving beta-blockade compared with patients receiving placebo (22),(25) or conventional therapy (23) (salt supplementation) in the 2 small RCTs. The overall efficacy for ivabradine was 64% (95% CI, 47%-80%; I^2=24.7%, P=.25) (Figure 2.2 [C]). (111),(147) There is a lack of head-to-head studies between ivabradine and beta receptor blockade for the treatment of POTS. However, the negative beta-blockade RCT and the higher proportion of treatment-resistant patients in the ivabradine case series suggest that ivabradine may be superior. An RCT adequately powered to compare these different rate-controlling strategies in both hyperadrenergic and neuropathic cohorts may help clarify the role of these agents in the treatment of POTS.

Legend Table 2.2: Heart Rate Reduction[a]

[a]bid = twice daily; NA = not available; OD = once daily; SF-36 = 36-item Short Form Health Survey; tid = 3 times per day; WFDI = Walker Functional Disability Inventory; WSS = Winker symptom scale

[b]Heyland Methodological Quality Score of 8 or greater denotes high quality; all other studies graded 4 using the rating score modified from the Oxford Centre for Evidence-Based Medicine represent case-series or case-controlled studies

[c]Patients may be utilizing other therapies e.g. dietary salt & water

[d]Dosage not reported

Table 2.2: Heart Rate Reduction[a]

Reference, Year	Total patients in study (No.)	Patients included in efficacy calculation (No.)	Patients excluded from efficacy calculation (No.)	Age (y) mean	Female Sex (%)	Treatment	Trial design	Symptom tool	Efficacy (%)	Follow-up (d)	Evidence Grade/ Quality
Cardioselective beta-receptor blockers											
Chen et al,(23) 2011	53	19	0	12	58	Metoprolol 0.25 mg/kg bid	RCT	WSS	58	132	8[b]
Freitas et al,(142) 2000	11	10	0	31	100	Bisoprolol 5 mg OD	Case series[c]	None	70	42	4
Lai et al,(138) 2009	121	14	Unknown	15	79	Metoprolol (n=12)[d] Atenolol (n=2)[d]	Case series[c]	WFDI	57	NA	4
Lin et al, (143) 2015	61	34	0	12	47	Metoprolol 12.5 mg bid	Case series	WSS	71	90	4
Zhang et al,(144) 2014	27	25	2	11	52	Metoprolol 0.25 mg/kg bid	Case series	WSS	52	90	4
Zhao et al,(145) 2014	74	49	0	12	49	Metoprolol 0.5 mg/kg bid	Case series	WSS	57	68	4
		151		**16**					**61**		
Non cardioselective beta-receptor blockers											
Abe et al,(146) 2000	10	7	0	20	71	Propranolol 10mg tid (n=6) atenolol 25mg OD (n=1)	Case series	None	71	NA	4
Fu et al,(22) 2011	34	9	0	27	89	Propranolol 80 mg OD	RCT	SF-36	33	28	9[b]
		16		**24**					**68**		
Ivabradine											
McDonald et al,(111) 2011	22	20	2	35	85	Ivabradine 2.5-15mg/d in 1-2 doses	Case series[b]	None	55	>140	4
Sutton et al,(147) 2014	25	25	0	33	84	Ivabradine 5-20 mg/d in 1-2 doses	Case series[b]	None	72	450	4
		45		**34**					**64**		

Miscellaneous therapies

The 3 exercise intervention studies included a small RCT (31 patients) (107) and 2 case series (Table 2.3). (22),(104),(148) The 15 patients in the control arm of the RCT were well matched to the 16 patients undergoing a 3-month program of jogging. Both groups had access to the same army diet and undertook similar activities, with the treatment group also performing 30-minute jogging sessions 3 times each week (gradually increased to 50 minutes per session by the third month) at a speed tailored to maintain the target training heart rate, defined as resting heart rate + 0.6 x (maximal - resting heart rate). Efficacy of exercise training in the RCT of male army recruits was 63%. (107) In the first case series (with information presented in 2 separate publications), 25 participants were enrolled in a supervised exercise program (accompanied by advice to increase salt and water intake). (22),(104) The reported 100% efficacy for the 3-month exercise intervention was based on the physical component sub-score of the 36-item Short-Form Health Survey (SF-36). However, note that only 19 participants (of the original 25 enrolled in the study) completed the program and that 23% of those, in whom the social functioning sub-score of the SF-36 was recorded, indicated no improvement or deterioration. (22),(104) The second case series included 251 POTS registry patients provided with an exercise program with no direct supervision. (148) This registry study did not report on treatment efficacy according to the number of patients responding. Response data were available from only 78 participants (31% of the original cohort of 251 participants enrolled), making it difficult to place too much weight on the 100% efficacy reported in each of the SF-36 sub-scores. (148) The overall efficacy of the exercise intervention (not including the registry study) was 72% (95% CI, 55%-86%; I^2=6.3%, P=.30) (Figure 2.2 [E]).

Two case series have been published on the use of erythropoietin to manage symptoms in patients with POTS (Table 2.3). The smaller series combined erythropoietin with iron supplementation and reported improvement in 3 of the 8 patients. (149) The larger case series was a retrospective medical record review in which 71% efficacy was reported in a treatment-resistant population. (118) The group reporting on a retrospective chart review of outcomes after droxidopa therapy also reported on outcomes after an acetylcholinesterase inhibitor (pyridostigmine), (120) a dopamine reuptake inhibitor (modafinil) (119) and a catecholamine uptake inhibitor (methylphenidate) (120) with respective efficacy of 51%, 60% and 77%, respectively (Table 2.3). Thirty-five patients (17%) treated with pyridostigmine stopped taking the medication due to adverse effects (mainly gastro-intestinal). Four of 7 patients treated with a closed auditory loop stimulation reportedly improved, (150) whereas the case series of patients treated with sinus node modification reported no symptomatic improvement despite a reduction in heart rate (Table 2.3). (115)

Table 2.3: Miscellaneous Therapeutic Approaches[a]

Reference, Year	Total patients in study (No.)	Patients included in efficacy calculation (No.)	Patients excluded from efficacy calculation (No.)	Mean Age (y)	Female (%)	Treatment	Trial design	Symptom tool	Efficacy (%)	Follow-up (d)	Evidence Grade/ Quality
Exercise											
Fu et al, 2010(104) 2011(22)	34	19	6	26	95	Endurance + resistance, 3 mo[b]	Case series	SF-36	77	90	4
George et al,(148) 2016	251	78	173	26	84	Endurance + resistance, 3 mo[b]	Case series	SF-36[c]	NA[d]	90	4
Winker et al,(107) 2005	31	16	0	21	0	Endurance, 3 mo[e]	RCT	WSS	62.5	90	11[e]
		113		**25**					**70**		
Erythropoietin											
Hoeldtke et al,(149) 1995	8	8	0	35	75	EPO 50 IU/kg 3x/wk SC + FeSO4	Case series	None	38	63	4
Kaniwal et al,(118) 2012	200	39	NA	33	95	EPO 10–20,000 IU weekly, SC[b]	Case series	None	71	180	4
		47		**34**					**55**		
Miscellaneous											
Fortunato et al,(150) 2016	^	7	0	17	57	Closed loop auditory stimulation, 10-16x over 8-17 d	Case series	SQ (14)	57	14	4
Kaniwal et al,(121) 2011	203	168	35	26	88	Pyridostigmine 30 -90 mg bid or tid OR 180mg SR daily[b]	Case series	None	51	360	4
Kaniwal et al,(120) 2012	24	18	6	28	83	Methylphenidate, 10mg tid	Case series	None	77	270	4
Kaniwal et al,(119) 2011	85	60[f]	25	29	87	Modafinil 100-200mg	Case series	None	60[f]	270	4
Shen et al,(115) 2001	7	7	0	41	100	Sinus node modification	Case series	SQ (10)	0	960	4

Legend Table 2.3: Miscellaneous Therapeutic Approaches[a]

[a]bid = twice daily; EPO = erythropoietin; FeSo4 = ferrous sulfate 300mg tid; NA = not available; RCT = randomized controlled trial; SC = subcutaneous; IU = international units; SQ(10), SQ (14) = symptom questionnaire rating 10 and 14 symptoms respectively; SF- 36 = 36-item Short Form Health Survey; SQ (10), SQ(14) = symptom questionnaire rating 10 and 14 symptoms, respectively; SR = slow release; tid = 3 times per day; WSS = Winker symptom scale (48)

[b]Combined with increased salt and water and raised head of bed;

[c]A total of 78 of 205 patients (31%) completed the SF-36

[d]Results reported by symptoms rather than by individual

[e]Heyland Methodological Quality Score ≥8 denotes high quality; all other studies graded 4 with the Oxford Centre for Evidence-Based Medicine represent case-series or case-controlled studies;

[f]A total of 41 of 60 patients with orthostatic intolerance had postural tachycardia syndrome on orthostatic stress testing, but results are not reported separately for the subgroup of patients with postural tachycardia syndrome

Discussion

This systematic review identified 28 publications describing symptomatic responses after at least 4 weeks of treatment in 858 patients with POTS with the following key findings. First, there is a paucity of RCT data, with efficacy information from only 103 patients randomized in the 3 RCTs. (22),(23),(107) Second, therapy directed at intravascular volume expansion or heart rate reduction was associated with similar mean rates of efficacy (60-70%) in treatment-naive patients from both case series and limited RCT data. Third, the evidence for use of vasopressors in patients with POTS primarily involves use of low doses of midodrine in children, with the mean efficacy of approximately 65%. Fourth, exercise training seems efficacious in approximately 70% of patients with POTS who can tolerate the regimen. Last, a host of miscellaneous therapies have been given to small cohorts of treatment -resistant patients to variable effects. Many of the medications directed at increasing intravascular volume or vascular tone and controlling heart rate are relatively standard therapies for patients with POTS, as reported in several large series. (123–126, 151) This review identified an overall limited evidence base for POTS therapies, with significant heterogeneities seen in terms of age and symptom severity of included patients and the measures used to determine treatment efficacy.

Tolerability of POTS Therapies

Whilst reviewing treatment efficacy, we noted that the occurrence of adverse events and adverse effects were rarely reported. The efficacy estimates are predominantly based on the outcome of patients who continued the intervention rather than by intention to treat.

Patients who ceased therapy are likely to have done so due to either lack of effect or experiencing an adverse effect. It is likely, therefore that omitting to report intention to treat numbers has inflated efficacy results. Publication bias may also have contributed to an overestimate of efficacy in the case series as suggested by the greater benefit from beta-receptor blockade in the case series than that seen in the RCT of propranolol. (22, 23)

Evaluating Response to Therapy: Need for a Standardized Tool

Notably, 11 of the 28 publications did not use any tool to measure symptomatic response, relying on retrospective review of standard clinical assessment. The remaining studies used a variety of questionnaires for assessing symptomatic response to therapies, with a variable emphasis on QOL domains and frequency or severity of symptoms. The SF-36 sub-scores for physical and social functioning were used to assess symptomatic outcomes in 4 studies. (22),(104),(112),(148) Two studies adopted alternative tools for assessing QOL. The first of these used a questionnaire developed at the Children's National Health System that consisted of 25 questions in 8 major domains. (137) The single-centre retrospective postal survey of patients who had previously undergone autonomic reflex testing used the Walker Functional Disability Inventory, which contains 15 questions related to daily activities. (138) Eight studies based efficacy assessment on scores generated by summing the frequency of symptoms. Six of these used a scale validated for adults during occupational assessments, referred to in tables 1 through 4 as the Winker symptom scale (WSS). (23),(107),(139),(143),(144),(145) Similar study-specific tools were used in the other 2 studies. (115),(136) Three studies used tools assessing the severity of symptoms, including study-

specific questionnaires (29),(141),(150) and the Orthostatic Hypotension Questionnaire, (112) previously validated for adults with neurogenic orthostatic hypotension. (49)

Objective assessment of symptomatic response to POTS therapies using reliable and validated QOL questionnaires is important because it is well recognized that the correlation between physiologic data, such as orthostatic heart rate increment, and a patient's severity of symptoms is highly variable. (154) Favourable symptomatic response may not be accompanied by the control of heart rate. Furthermore, reduced orthostatic heart rate increase may not beget symptomatic improvement. (22, 115) Symptoms in many patients with POTS may improve over time regardless of therapy. (123) Several confounders may also interfere with assessment of the true treatment efficacy, including the potential for placebo effects and the inadequacies of some of the symptom tools used. Standardization of QOL and symptom burden tools used at baseline and endpoint analysis will greatly improve our ability to evaluate the efficacy of various interventions over time.

Refining POTS Therapies: Potential Role of Biomarkers

Due to heterogeneity in the pathophysiology underlying POTS, biomarkers may play an incremental role in refining therapy. For example, an RCT found that midodrine was superior only to placebo in reducing orthostatic heart rate increase in the subgroup of patients with peripheral venous pooling (based on calf blood flow measures). (64) Other biomarkers that may be useful in delineating responders to specific therapy include plasma C-type natriuretic peptide,(143) noradrenaline,(144) copeptin, pro-adrenomedullin(139) and measures of plasma volume and 24-hour urinary salt excretion. (145) Further studies are

needed to validate these and other novel biomarkers that may guide the physician in choosing the best individualized treatment option.

Need for Improved Collaborative Research

This lack of quality data on the efficacy of various therapies for POTS is in keeping with the obvious lack of class I recommendations or Level A evidence in the recent expert consensus statement from the Heart Rhythm Society. (109) Of note, the class IIa recommendation of acute IV infusion for short-term clinical decompensation has a low level of evidence and is derived from studies with less than 4 weeks of follow-up that are not included in this review. (54),(156),(157),(158) Evidence has become available since the publication of the consensus statement, regarding regular IV saline infusions via long-term or repeated IV cannulations that conferred high efficacy in treatment-resistant patients. (112) Most of the consensus statement recommendations are at class IIb (benefits equivalent to or possibly exceeding harm), with several stemming from consensus opinions rather than from published evidence. The management of POTS in the real world is likely to be highly variable and physician dependent. With the lack of quality data, the outcome of patients with POTS can vary greatly, hinging on the experience of the treating physician.

Although the consensus statement may help to guide therapies, this review highlights the urgent need for more systematic and collaborative research as well as shared patient registries to improve the evidence base for POTS therapies. (24) We suggest that future studies be designed to address the following considerations: (1) need for homogenous patient

groups in relation to pathophysiology (neuropathic vs. non neuropathic); (2) use of a standardized, validated questionnaire to assess severity and frequency of symptoms of orthostatic intolerance; (3) use of a quantitative measure of heart rate increment and symptoms of orthostatic intolerance during tilt or standing test; (4) monitoring of fluid and salt intake; (5) monitoring of exercise activity; (6) duration of follow-up of at least 6 months; and (7) use of biomarkers.

Conclusion

Good-quality evidence for the management of patients with POTS is lacking. Case series and small RCTs of interventions directed at increasing intravascular or blood volume, increasing vascular tone, controlling heart rate, and increasing exercise tolerance demonstrate moderate efficacy. More research is urgently needed to improve the evidence gap in the management of this complex condition.

Chapter 3: Brain Fog in Postural Tachycardia Syndrome: An Objective Cerebral Blood Flow and Neurocognitive Analysis

Statement of authorship: Brain Fog in Postural Tachycardia Syndrome: An Objective Cerebral Blood Flow and Neurocognitive Analysis

Brain Fog in Postural Tachycardia Syndrome:

An Objective Cerebral Blood Flow and Neurocognitive Analysis

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Contextual Statement

In this chapter, our pilot study is described. In this pilot study, we followed a protocol used in a study of neurovascular coupling in which patients with spinal cord injury were found to have a less robust increment in posterior cerebral blood flow velocity in response to a visual stimulus when compared with a control group. (1) The difference in CBFv response was attributed to disruption of autonomic reflexes in the cohort with spinal cord injuries. As patients with POTS report significant symptom scores related to autonomic function, we undertook this study to identify if patients with POTS had similar deficits to those seen in the patients with spinal cord injury. Using a handheld ultrasound probe to measure CBFv from the posterior cerebral artery during brief visual stimuli, we did not find any difference between CBFv responses in the POTS group when compared with the control group, however. In this study we also piloted a number of cognitive tasks, gaining insight into problems that might be encountered interpreting cognitive outputs when tasks were repeated.

Abstract

Background: Cognitive difficulty, often described as “brain fog”, is a prevalent complaint amongst patients with postural tachycardia syndrome (POTS). It remains unclear whether brain fog is related to impaired cerebral blood flow (CBF) in POTS.

Methods: We assessed CBF in the posterior cerebral artery (PCA), using transcranial Doppler ultrasound, in response to visual stimuli. CBF was recorded in 11 POTS subjects and 8 healthy controls whilst they rested with eyes closed in a seated position and following the direction to open their eyes. A series of neurocognitive tasks were then undertaken.

Results: CBF parameters were similar between the two groups. POTS patients demonstrated significantly longer latency in delayed match to sample response time and greater errors in attention switching task.

Conclusions: Impaired short-term memory and alertness may underlie the symptom of brain fog in POTS patients, despite normal CBF responses to visual stimuli.

Introduction

Postural tachycardia syndrome (POTS) is a chronic debilitating condition in which symptoms of orthostatic intolerance (OI) are accompanied by a sustained increase in heart rate >30 beats per minute (bpm) within 10 minutes of orthostatic challenge. (8),(78) Current available treatments for POTS demonstrate only moderate efficacy with limited evidence base. (9),(24),(109) Cognitive difficulty, often described as “brain fog”, is a prevalent complaint amongst patients with POTS. Ninety-six percent of the 138 patients with POTS responding to a questionnaire on the symptoms of brainfog indicated they had significant symptoms described as “forgetful”, “difficulty thinking”, “difficulty focussing”, “cloudy” and “difficulty finding the right words or communicating”. (81) Interestingly, brain fog has been reported to occur even in the supine position, and may not be limited to upright posture. (82) Others have demonstrated approximately 25% increase in cerebral blood flow (CBF) velocity in the posterior cerebral artery (PCA) of healthy individuals in response to visual stimuli. (1) However, the CBF pattern and its response to visual stimuli have not been investigated in POTS individuals while seated. Here, we hypothesized that POTS individuals have impaired CBF regulation as well as cognition to explain the symptom of brain fog when seated.

Methods

Consecutive patients with POTS (confirmed with 10-minute orthostatic challenge) and complaint of brain fog (difficulty thinking/focusing/communicating, forgetful and cloudiness) were studied. (81) All subjects remained on their usual POTS treatments (Table 3.1). Additionally, eight age-matched healthy volunteers, who were not on any regular medications, were studied. All subjects had abstained from caffeine or alcohol for 24 hours before the study. All studies were undertaken between late morning to mid-afternoon. Participants provided written informed consent. This study has institutional ethics approval.

Colour TCD with sonography was used to assess CBFv in the PCA. A 2MHz phased array, handheld transducer was used along with a portable ultrasound unit (SonoSite Edge, SonoSite Inc., Washington, USA). Participants were asked to sit quietly with their eyes closed for 1 minute. The temporal bone was used as an acoustic window. Using the duplex images, the echogenic thalami were located and used as a landmark from which the circle of Willis and subsequently the PCA was identified. The pulsed wave Doppler mode was used to generate a real-time image and spectral waveform of CBF. Measurements of CBF velocity were taken at baseline with eyes closed for 1 minute and for a 10-second interval after the subject was given the instruction “open your eyes”. This process was repeated five times with all recordings analysed for percentage changes, between eyes closed and eyes opened, in peak systolic velocity (PSV), end diastolic velocity (EDV) and time averaged peak (TAP). The TAP parameter represents the mean flow velocity over an integral number of cardiac cycles.

Each participant was then asked to complete a series of neurocognitive tests (CANTAB: Cambridge Neuropsychological Test Automated Battery, Cambridge Cognition Ltd., Cambridge, UK) to assess executive function, reaction time (RT), memory and attention. These tests are described in greater detail in Chapter 1 and video demonstrations of the tasks can be viewed online. (101) Briefly, they involved a test of RT in which subjects were instructed to touch a signal as quickly as possible as it appeared in different positions on the iPad screen. This was followed by: rapid visual information processing task (RVIP): when subjects were asked to identify pre-defined 3 digit sequences amongst rapidly appearing random numbers on the screen; delayed match to sample task (DMS): when subjects were asked to match a series of complex geometric coloured patterns with one of four patterns appearing on the screen after the target sample had been hidden for up to 12 seconds; and attention switching task (AST): when subjects were assessed on the ability to ignore irrelevant information when responding to a question. The total time taken to complete the assessment (including instructions and non-assessed training phases for each module) was approximately 45 minutes.

Data was analysed in GraphPad Prism 7 (La Jolla, California, USA). Data that was not normally distributed was analyzed using the Mann Whitney U test. Categorical data was compared using chi-square analysis. A single outcome measure for latency and errors was pre-defined for each neurocognitive task to avoid the need to use a Bonferroni (or similar) correction in interpreting the many outcomes provided by the CANTAB program. Statistical significance was taken as $p<0.05$.

Results

Nine of the 11 (82%) POTS patients were female compared with 4 of the 8 (50%) controls, with median age of 28 and 31 years old respectively (both p=NS). Detailed medications use is shown in the Table. Five of the 11 POTS patients were not on fludrocortisone, midodrine or heart rate slowing medications. Baseline PSV and percentage increment of all CBF velocity parameters with visual stimuli were similar in the PCA of POTS individuals versus healthy controls (Table; all p=NS).

POTS individuals had a significantly longer latency in DMS response (3.6 vs. 2.5 seconds, p=0.04) and achieved lower number of correct responses during AST as compared to healthy controls. However, the median latencies for the RT, AST, and RVIP tasks were not statistically significant (Table 3.1).

Table 3.1: Baseline characteristics, cerebral blood flow and neurocognitive test parameters

	POTS (n =11)	Controls (n = 8)	P value
Baseline characteristics			
Age, years (Median, IQR)	28 (19-37)	31 (26-35)	0.3
Female, n (%)	9 (82)	4 (50)	0.1
POTS medications, n (%) - Fludrocortisone - Midodrine - Ivabradine - Propranolol	 4 (36) 5 (45) 3 (27) 1 (9)	 - - - -	-
Baseline peak systolic velocity, cm/s (IQR)	54 (43-68)	49 (49-52)	0.8
Cerebral blood flow parameters: percentage increment with visual stimuli, % (Median, IQR)			
Time averaged peak	21 (15-27)	22 (16-24)	0.9
Peak systolic velocity	15 (12-21)	14 (9-18)	0.7
End diastolic velocity	21 (13-24)	17 (12-45)	0.9
Neurocognitive parameters: at rest and seated (Median, IQR)			
Reaction time, ms	214 (173-271)	227 (200-267)	0.4
Rapid visual information processing latency (ms)	437 (397-498)	437 (410-474)	0.8
Delayed match to sample - latency (ms) - number of correct response (n)	 3630 (3029-4395) 4 (3-5)	 2482 (1754-3295) 5 (4-5)	 0.04 0.12
Attention switching task - latency (ms) - number of correct response (n)	 463 (425-468) 156 (152-157)	 445 (414-487) 159 (158-160)	 0.6 0.004

IQR: inter-quartile range. Neurocognitive tests: the reaction time is the time taken to touch a signal as quickly as possible as it appeared in different positions on the iPad screen. The rapid visual information processing test involved identification of pre-defined 3 digit sequences amongst rapidly appearing random numbers on the screen. The delayed match to sample test instructs the subject to identify which of 4 images provided matches the target image shown previously. The attention switching task instructs the subjects to touch the correct response to answer a prompt work that appears above an arrow. It measures the subject's ability to ignore irrelevant information when responding to a question. Latency is the time taken to touch the correct response.

Discussion

This study demonstrated objective evidence of neurocognitive deficits in POTS individuals but similar increment in CBF velocity parameters in response to visual stimuli in the PCA of both groups. Others have demonstrated a correlation between increment in CBF in the middle cerebral artery (MCA) during cognitive challenge (functional hyperaemia) and the ability of POTS patients to recall numbers. The deficit in functional hyperaemia became much more pronounced when the cognitive challenge was performed concurrently with orthostatic challenge, suggesting impairment of both neurovascular coupling and autoregulation. (82) Autoregulation is the maintenance of a relatively constant cerebral perfusion pressure despite significant fluctuations in peripheral blood pressure. Autoregulation tends to deteriorate in patients with POTS during orthostatic challenge, as oscillations in peripheral blood pressure become more marked. (82),(83) We found normal CBF velocity response in the PCA to visual stimuli in POTS patients whilst remaining seated. However, it remains unknown whether CBF changes would differ if measured in other vessels, such as the MCA, or with more complicated visual search paradigms. (159)

There has been an increasing awareness of cognitive dysfunction in POTS patients. To date, formal neurocognitive assessments in POTS patients remain limited with variable findings of deficits in memory, attention and executive function using different neuropsychological testing tools. (160) We found deficits in short-term memory and alertness in our POTS cohort in the seated position. In contrast, others have shown impaired selective attention and cognitive processing but unaffected memory in POTS patients using different neuropsychological tests. (161) This may be due to the heterogenous nature of the condition

and the many factors such as sleep disturbances, chronic fatigue and medication use, that may influence different facets of the cognitive status. These objective measures of cognitive dysfunction may in part explain the brain fog described by POTS patients even when recumbent, although the mechanisms remain unclear. (81)

Study limitations

We used a portable ultrasound setup with a handheld transducer to assess the ability to detect changes in CBFv during the brief period in which changes in blood flow occur in response to the increase in cerebral metabolic demand following the visual stimulus of opening the eyes. Headgear fixation of the ultrasound probe would have provided the additional ability to measure changes in CBFv during the prolonged period of cognitive testing but would have changed the test from being a widely accessible clinical tool to the less accessible research measure.

Using the MCA instead of the PCA may have increased the reliability of maintaining a constant angle of insonation. However, the increment in CBFv in the PCA following a visual stimulus is much greater than in MCA, not only because of the smaller diameter of the vessel, but because the visual cortex is supplied by the PCA. The 21% increment in the PCA CBF velocity following visual stimuli seen in our study is in keeping with a previously published figure of 25% seen in healthy controls.[8] This magnitude of change seen in the PCA warrants its selection over the larger and technically easier MCA, where the comparative change is much lower at 4%.[7]

Although hypocapnia can alter cerebral and peripheral vascular tone, it is unlikely that measurement of end-tidal carbon dioxide (ETCO2) levels would have contributed greatly to our study as the simple eye opening task and the brevity of the period during which the eye-opening stimulus effects CBFv (maximal during the first 10 seconds) is unlikely to have resulted in significant changes in ETCO2.

It is unclear if the continued administration of the usual POTS medications may have altered the CBFv changes in response to visual stimuli. Discontinuation of these medications may itself have skewed results as discontinuation can precipitate rebound changes in intravascular volume, HR and vascular tone which could also have confounded interpretation of CBFv responses to stimuli. Furthermore, the removal of therapeutic agents may have overemphasized differences in cognitive performance between POTS and control groups. The decision to continue treatment allowed us to identify differences in cognitive ability between POTS and control groups even with maximal therapy. We acknowledge that factors for which we did not control including education level, intelligence, sleep deprivation and mental health conditions may have contributed to the differences seen in results from cognitive assessment. (162) In addition, there may be greater cerebral activation with less lateralisation in females. (163) The lack of significance in some cognitive parameters may be due to the small number of POTS subjects in this study.

Conclusion

POTS patients demonstrate normal CBF velocity increment in response to visual stimuli when seated. Impaired short-term memory and alertness may reflect the symptom of brain fog in POTS patients.

Chapter 4: Cerebral blood flow and cognitive performance in postural tachycardia syndrome: Insights from sustained cognitive stress test

Contextual Statement

During the pilot study we had noted the POTS group became notably fatigued whilst performing cognitive tasks. We wished to determine if the prolonged cognitive stress was associated with a deterioration in cerebral blood flow response to the prolonged cerebral metabolic demands. We had measured CBFv changes in the PCA during the pilot study, which was appropriate to the cerebral regions activated by the brief visual stimulus and the expectation of a robust increase in CBFv as reported by others (>20% increase in CBFv in the PCA) when compared with the MCA (~3% increase in CBFv in the MCA). (1)

In this study, changes in CBFv in the middle cerebral artery (MCA) was measured despite the expectation that the relative change in CBFv associated with cerebral activation would be lower in the MCA than in the PCA. This decision was based on both the fact that the larger diameter of the MCA would improve our ability to maintain a constant angle of insonance (critical in comparing changes in CBFv over time), as well as the knowledge that the cerebral region supplied by the MCA would be activated during cognitive stimuli.

We maintained the angle of insonance in the MCA through use of headgear fixation. The equipment utilized to record the physiological changes during the prolonged cognitive stress required the use of a dedicated facility. In comparison, during the pilot study, we were able to adapt readily to facilitate measurement of CBFv in a variety of settings through the

use of a portable ultrasound and handheld probe. The dedicated facility had the additional advantage of allowing simultaneous recording of participants' heart rhythm, respiratory rate and end tidal carbon dioxide (ETCO2), which allowed us to determine if hypocapnia was contributing to changes in CBFv.

In the development of this study protocol, a decision was made to allow patients to continue their usual medications with the exception of the short acting vasopressor, midodrine. We excluded midodrine on the basis that the short half-life resulted in complete washout of the vasopressor every night . We did not, therefore, expect to see any rebound changes in CBFv responses by withholding this medication. The rapid onset of action of midodrine also lent itself to a direct study of the vasopressor's effect on CBFv in response to prolonged cognitive stress (reported in Chapter 5). By allowing patients to continue their other medications we may have increased the chance of creating a difference between the groups as a result of reduced sympathetic activation (in the case of beta-blockade), or impaired concentration (in the case of anti-anxiety or anti-depressant medications). Ceasing these medications may have also clouded interpretation of our results, however, as withdrawal of beta-blockade may result in rebound tachycardia, and withdrawal of anti-anxiety or anti-depressant medications may impair cognitive performance through sleep deprivation and mental health consequences. Bearing this in mind, we opted to allow patients to continue these medications. We did not measure sleep deprivation or level of education in our study, both of which may have impacted on cognitive performance.

We demonstrated a greater fall in CBFv in the MCA in the POTS group during the course of prolonged cognitive stimulus, however the magnitude of fall was significantly less

than the 50% reduction in CBFv previously quoted as the change likely to produce cerebral hypoperfusion,(96) which may reflect the more subtle changes in cognitive ability as opposed to syncope, which was the condition under study by this group.

Introduction

Individuals with postural tachycardia syndrome (POTS) often experience a number of debilitating cardiovascular, gastrointestinal and neuropsychologic symptoms in addition to their intolerance to standing. (164) Although it is quite clear that symptoms are related to the assumption of upright posture in these individuals,(26) a myriad of factors that reduce blood volume (104),(165) 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. (26),(164),(166) The impact of these symptoms on quality of life and cognitive dysfunction has been well described, however treatment options remain limited. (9) Correction of dehydration, exercise training, and manipulation of vasoactive and heart rate slowing medications may provide some symptomatic relief, however improvement in therapeutic approach will require a better understanding of the underlying heterogenous pathophysiology. (9),(109)

Cognitive dysfunction in patients with POTS is sometimes attributed to concurrent anxiety and depression, (167) although performance in tasks requiring sustained attention and short term memory has also been shown to deteriorate with orthostatic stress. (82),(167) The association of cognitive dysfunction with upright posture may relate to a more pronounced reduction in cerebral blood flow (CBF), (98) or oscillations in blood pressure and

CBF velocity (CBFv). (82) However, the persistence of mental fatigue and cognitive disturbances ("brain fog") even in a recumbent position, have been reported in POTS. (161) It remains unclear whether these symptoms can be explained by abnormal cerebral perfusion in the absence of orthostatic stress. We therefore hypothesize that CBFv is reduced in POTS patients 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 prolonged (30 minutes duration) cognitive stress whilst seated as well as after orthostatic stress (5 minutes standing) in consecutively enrolled participants with POTS (POTS group). (Figure 4.1) We compared these with a cohort of 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 prior to their inclusion in the study.

Study eligibility and enrolment

POTS individuals 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 heart rate of >30 bpm during HUT or within 10 minutes of standing, without a postural blood pressure drop of >20 mmHg. These symptoms included light-headedness, headache, fatigue, neurocognitive deficits, palpitations, nausea, altered vision, shortness of breath, or sensation

of heat while upright, with no other medical explanation for the symptoms. All POTS patients were on treatment in accordance with current guidelines. (109) There were no clinical exclusion criteria. The control group consisted of age- and sex-matched healthy volunteers with no known cardiac or autonomic symptoms.

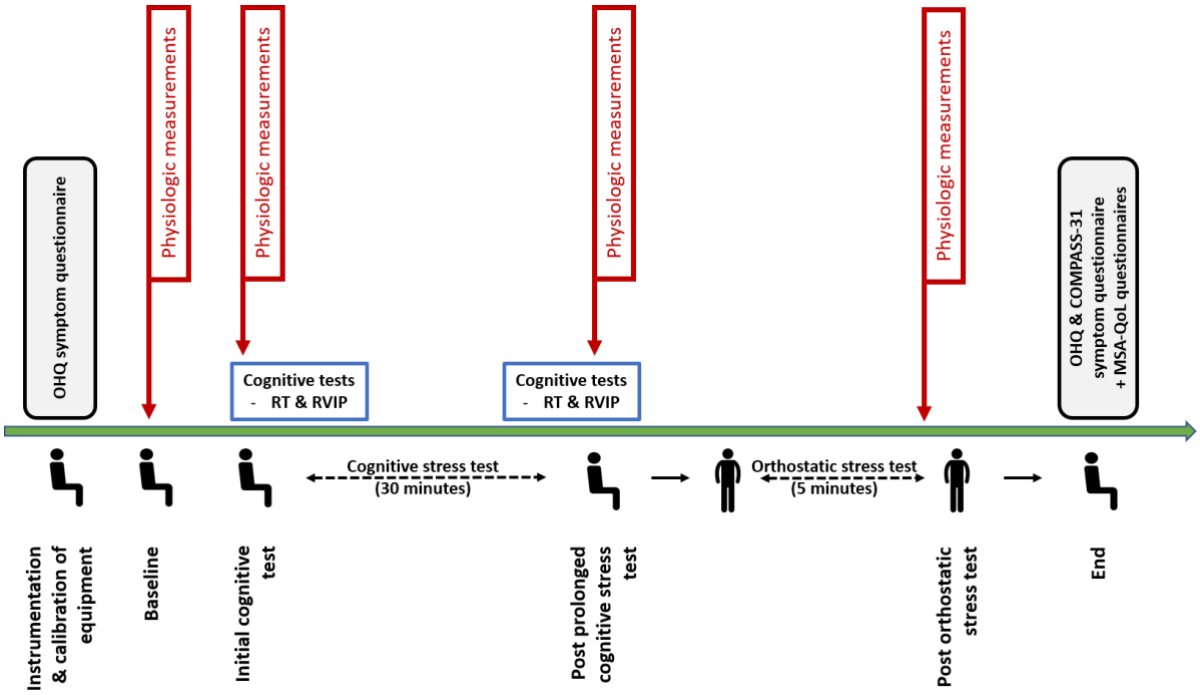


Figure 4.1: Study Protocol

Sequence of physiologic and cognitive measurements during the entire study protocol.

RT: reaction time, RVIP: rapid visual information processing, OHQ: orthostatic hypotension questionnaire, COMPASS-31: Composite Autonomic Symptom Score-31, MSA-QoL: Multiple System Atrophy-Quality of Life.

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 interpretation of the study results. The study protocol was performed in a climate-controlled facility (22°C), with participants seated 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 (MCA) 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. CBF velocity was recorded continuously throughout the study protocol. A single-lead electrocardiogram (FE132 Bioamp, ADInstruments Pty Ltd, NSW, Australia) was placed for continuous monitoring. Continuous, non-invasive beat-to-beat hemodynamics (heart rate; HR, blood pressure; 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 (RR). 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, electrocardiogram, beat-to-beat BP waveform & heart rate, $ETCO_2$ 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 was 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). (101) Specifically, we assessed the cognitive domains of psychomotor speed and attention by measuring reaction time (RT) and rapid visual information processing (RVIP) 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 RVIP 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 RVIP were measured at baseline and after 30 minutes of prolonged cognitive stress test (PCST) (Figure 4.1).

The two CANTAB 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. Data are presented as mean ± standard deviation or median (Q1, Q3). OHSA is the symptom assessment component of the OHQ questionnaire used to quantify symptoms present at the time the questionnaire was completed. (49) Six symptoms are given a score from 0 (symptom not present) to 10 (most severe), with a maximum total score of 60. The COMPASS-31 (adjusted) score is a validated score calculated from the raw COMPASS 31 score after applying a weighting that takes into account the number of points and relative importance of organ systems to the assessment of autonomic dysfunction. (47) A high score indicates greater severity of symptoms related to autonomic dysfunction. The MSA-QoL score assesses factors that impact on quality of life with a high score indicating significant impairment in quality of life. (168)

Symptom assessment

In order to assess acute changes in symptoms we asked participants to rate their symptoms using the Orthostatic Hypotension Questionnaire (OHQ) (49) with the Likert scale (from 0-10; least to most severe), at baseline and after the prolonged cognitive stress testing. The symptoms assessed were: dizziness, light-headedness or feeling faint; problems with vision (blurring, seeing spots, tunnel vision); weakness; fatigue; trouble concentrating; and head & neck discomfort. While the OHQ 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. The MSA-QoL (Quality of life assessment in Multiple System Atrophy) questionnaire was used to assess quality of life. (168) Although not specifically designed for POTS, it has been well validated as a patient reported

outcomes tool. Further, autonomic symptoms were assessed using the well validated, abbreviated Composite Autonomic Symptom Score (COMPASS- 31). (47)

Statistical Analysis

Normally distributed variables were presented as mean ± standard deviation 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 seconds at the following time points for comparison: at baseline whilst seated, whilst undertaking the initial cognitive testing 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 vs. initial cognitive test, initial cognitive test vs. post PCST, baseline vs. orthostatic stress) as main effects and 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 n=22 with POTS and n=18 healthy sex- and age-matched controls. Baseline characteristics such as medication usage, seated physiologic and cerebral blood flow parameters are presented in *Table 4.1*. Notably, the POTS group has

higher resting HR whilst seated than the controls (90±14 vs. 74±9 bpm; p=0.01). There was no difference in mean resting BP, RR, $ETCO_2$ and CBFv between the groups whilst seated at rest.

Table 4.1: Baseline Characteristics

	POTS (n=22)	**Controls (n=18)**	**P value**
Clinical characteristics			
Age (y*ears*)	29±11	28±13	0.8
Female, n (%)	19 (86)	13 (72)	0.4
Medications, n (%) - Fludrocortisone - Ivabradine - Propranolol - Midodrine	 6 (27) 5 (23) 7 (32) 11 (50)	 0 (0) 0 (0) 0 (0) 0 (0)	-
Physiologic measurements (at rest and seated)			
Heart rate (*bpm*)	90±14	74±9	0.01
Systolic BP (*mmHg*)	112±12	110± 9	0.6
Diastolic BP (*mmHg*)	78± 12	78±10	0.9
Pulse pressure (*mmHg*)	34±11	32±7	0.7
Respiratory rate (*breaths/min*)	17±3	17±3	0.7
$ETCO_2$ (*mmHg*)	35±4	36±3	0.4
CBFv (c*m/s*)	63.0±13.9	65.3±13.3	0.8
Quality of life & 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 - Non-motor - Emotional **Total**	 13 ± 10 25 ± 9 20 ± 11 58 ± 25	 0 ± 1 4 ± 5 5 ± 9 9 ± 13	 <0.001 <0.001 <0.001 <0.001

POTS: postural tachycardia syndrome, BP: blood pressure, $ETCO_2$: end-tidal carbon dioxide, CBFv: cerebral blood flow velocity, OHSA: Orthostatic Hypotension Symptom Assessment, OHQ: Orthostatic Hypotension Questionnaire, COMPASS-31: Composite Autonomic Symptom Score-31, MSA-QoL: Multiple System Atrophy-Quality of Life.

Physiologic changes with initial cognitive testing

Mean HR was consistently higher in the POTS group (p=0.003) with significant increase during initial cognitive testing in both groups (p<0.001) but the extent of increase differed between POTS and Control groups (p=0.01, Table 4.2) with a greater increase seen in the Control group (9.5 vs. 4.4%, Figure 4.2 A). However, all other physiologic responses (BP, ETCO2 and CBFv) did not differ between groups from baseline to during initial cognitive testing (all p≥0.2, Table 4.2) despite significant increases in systolic & diastolic BP (both p<0.001) and CBFv (p=0.006) in both groups (Figure 4.2 B-D).

Legend Table 4.2: Physiologic and cognitive parameters with cognitive challenges

P value*denotes comparison between POTS and Control groups from baseline to initial cognitive testing, P value# denotes comparison between POTS and Control groups from initial cognitive testing to post prolonged cognitive stress test, POTS: postural tachycardia syndrome, BP: blood pressure, $ETCO_2$: end-tidal carbon dioxide, CBFv: cerebral blood flow velocity. RVIP: rapid visual information process, no.: number, Data are presented as mean ± standard deviation.

Table 4.2: Physiologic and cognitive parameters with cognitive challenges

	POTS (n=22)			Controls (n=18)			P value*	P value#
	Baseline	Initial cognitive testing	Post prolonged cognitive stress test	Baseline	Initial cognitive testing	Post prolonged cognitive stress test		
Physiologic measurements								
Heart rate (bpm)	90±14	94±15	92±15	74±9	81±10	79±10	0.01	0.7
Systolic BP (mmHg)	112±12	119±14	124±19	110±9	121±15	118±16	0.3	0.06
Diastolic BP (mmHg)	78±12	84±11	87±16	78±10	86±11	85±14	0.2	0.1
Pulse pressure (mmHg)	34±11	35±12	37±12	32±7	35±13	34±11	0.8	0.2
$ETCO_2$ (mmHg)	35±4	36±4	35±5	36±3	37±3	36±4	0.9	0.9
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	0.4	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	-	0.1

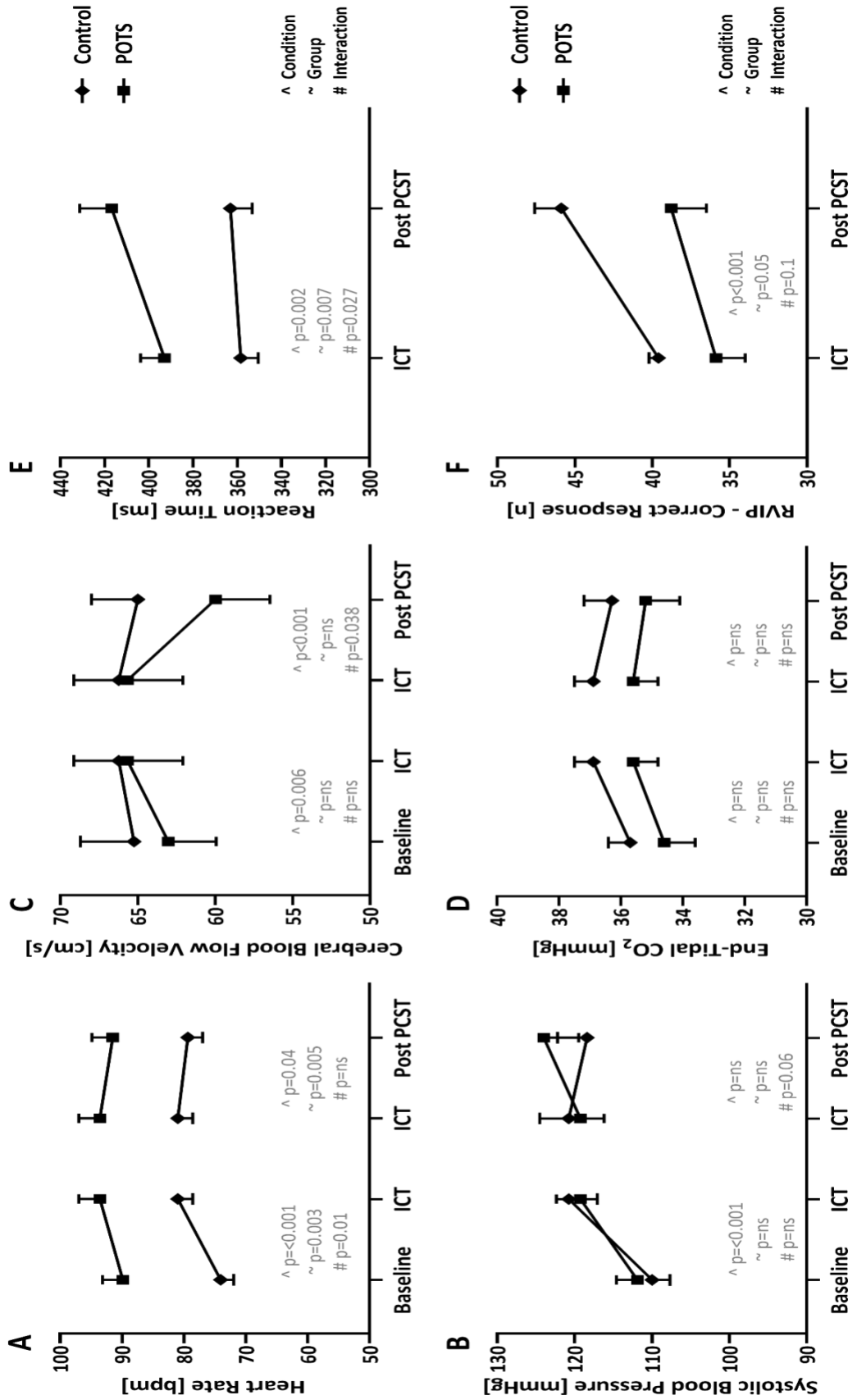
Physiologic and cognitive changes during repeat cognitive testing after PCST

HR response during repeat cognitive testing after PCST was similar between groups (p=0.7, Table 4.2) with consistent slowing as compared to during initial cognitive testing (p=0.04), although POTS patients maintained higher HR than Control patients throughout (p=0.005, Figure 4.2 A). Following PCST, CBFv was lower on repeat cognitive testing (p<0.001) when compared to during initial cognitive testing and significantly differed between groups (p=0.038, Table 4.2) with a larger decrease seen in the POTS patients (-7.8 vs. -1.8%, Figure 4.2 C). All other physiologic responses (BP & ETCO2) did not differ between groups during initial and repeat cognitive testing after PCST (all p>0.05, Table 4.2, Figure 4.2 B &D).

Legend Figure 4.2: Physiologic and cognitive parameters with cognitive challenges
The p values in each graph denote comparisons for ^condition (baseline vs. ICT or ICT vs. post PCST) in both groups, ~group (POTS vs. Control) and #interaction (between condition and group). For ease of illustration, all values plotted are mean ± standard error of the mean with uni-directional error bars.

POTS: postural tachycardia syndrome, ICT: initial cognitive test, PCST: prolonged cognitive stress test, RVIP: rapid visual information processing.

Figure 4.2: Physiologic and cognitive parameters with cognitive challenges



The effects of PCST on psychomotor speed and attention are summarized in *Table 4.2*. Mean RT was consistently longer in the POTS group (p=0.007) with significant increase when repeated cognitive testing was performed following PCST in both groups (p=0.002); however, the extent of increase differed between POTS and Control groups (p=0.027, Table 4.2) with a longer delay in the POTS patients (6.1 vs. 1.4%, Figure 4.2 E). When cognitive testing was repeated after PCST, the number of correct responses in the RVIP test increased in both groups (p<0.001; Figure 4.2 F); however, the accuracy was consistently lower in the POTS group (p=0.05) with blunted improvement as compared to the Control groups that approached statistical significance (p=0.1, Table 4.).

Physiologic changes at end of 5-minute orthostatic stress

Orthostatic stress resulted in significant increases in HR (p<0.001), systolic BP (p=0.001) and diastolic BP (p<0.001) as well as significant decrease in CBFv (p=0.002) in both groups (Figure 4.3 A-D). Notably, HR was consistently higher in POTS patients (p=0.002; Figure 4.3 A) while the remaining physiologic parameters showed no differences (p≥0.3). However, 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 (p≥0.5, Table 4.3).

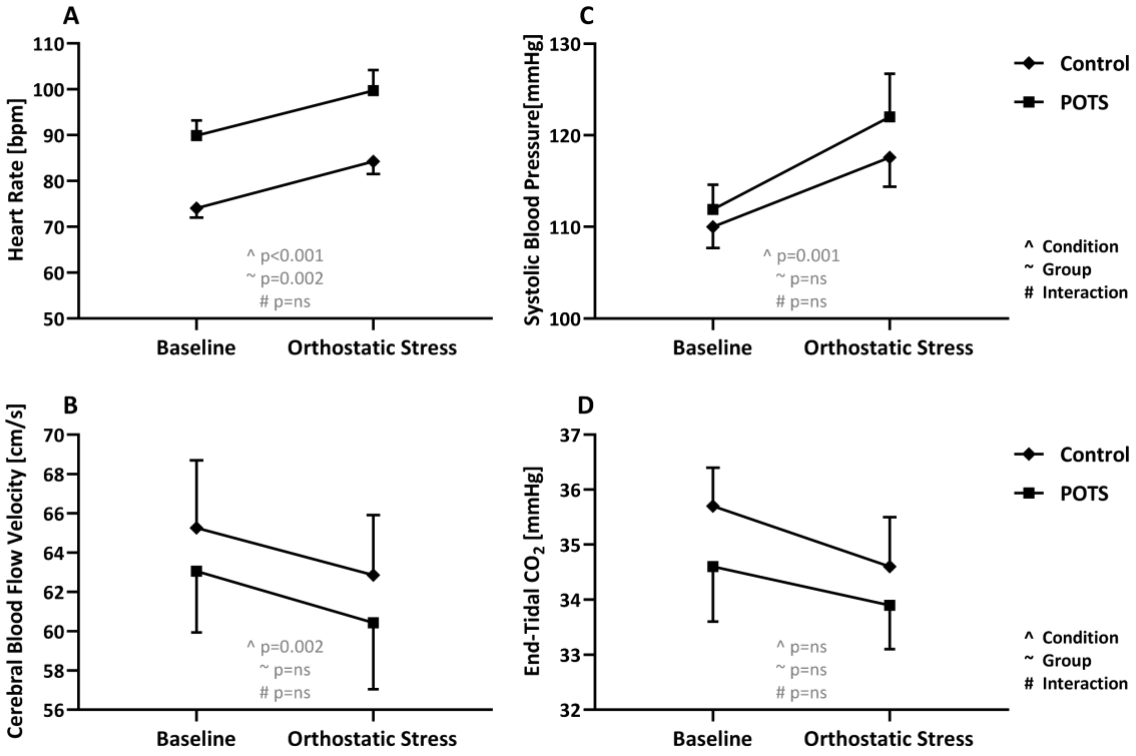


Figure 4.3: Physiologic changes with 5-minute orthostatic stress

The p values in each graph denote comparisons for ^condition (baseline vs. orthostatic stress) in both groups, ~group (POTS vs. Control) and #interaction (between condition and group). For ease of illustration, all values plotted are mean ± standard error of the mean with uni-directional error bars. POTS: postural tachycardia syndrome.

Table 4.3: Physiologic changes with 5-minute orthostatic stress

	POTS (n =22)		Controls (n = 18)		P value
	Baseline	Post orthostatic stress	Baseline	Post orthostatic stress	
Heart rate (bpm)	90±14	100±20	74±9	84±11	0.9
Systolic BP (*mmHg*)	112±12	122± 21	110±9	118±13	0.6
Diastolic BP (*mmHg*)	78±12	90±18	78±10	86±9	0.5
Pulse pressure (*mmHg*)	34±11	32±12	32±7	31±8	1.0
$ETCO_2$ (*mmHg*)	35±4	34±4	36±3	35±4	0.8
CBFv (cm/s)	63.1±13.9	60.4±14.8	65.3±13.3	62.9±11.8	0.6

P value denotes comparison between POTS and Control groups from baseline to post orthostatic stress, POTS: postural tachycardia syndrome, BP: blood pressure, $ETCO_2$: end-tidal carbon dioxide, CBFv: cerebral blood flow velocity. Data are presented as mean ± standard deviation.

Symptom and quality of life assessments

Overall quality of life scores (MSA-QoL) and symptom scores (COMPASS-31) were significantly higher in the POTS group in comparison to the Control group (*Table 4.1*). At baseline, orthostatic hypotensive symptoms were significantly higher in the POTS vs. Control groups ($p<0.001$, Table 4.1). The POTS group demonstrated consistently worse orthostatic symptoms ($p<0.001$) with 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) vs. 3 (1, 8) or +16 vs. 3 points, $p<0.001$].

Discussion

To our knowledge, this study is the first to evaluate CBFv in POTS individuals undergoing sustained cognitive challenge whilst seated. We found that following PCST, POTS individuals demonstrate cognitive dysfunction of reduced psychomotor speed which was accompanied by a significant reduction in CBFv when compared to healthy controls whilst remaining seated. Additionally, we found that both groups demonstrated similar reductions in CBFv and increments in heart rate 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, greater increase in orthostatic symptoms were reported by the POTS patients as compared to healthy controls at the completion of the entire study protocol. Taken together, the decline in CBFv in seated POTS individuals during repeat cognitive testing following PCST may explain the common symptom of mental clouding (‘brain fog’) in this patient population.

Cerebral blood flow and cognition in POTS

Systemic blood pressure and heart rate can vary enormously during periods of physical stress and orthostasis. It has been postulated that patients with POTS are unable to adequately buffer changes in the systemic circulation without compromising cerebral perfusion, termed autoregulation. (169) Several studies have evaluated the effect of orthostatic stress on cognitive function and cerebral hemodynamics in POTS patients. Ocon *et al*. found a decline in cognitive performance occurring with increasing orthostatic stress in patients with POTS and co-morbid chronic fatigue syndrome as compared to controls, that could not be explained by reduced CBFv. (83) In patients with chronic fatigue syndrome with 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. (170) During progressive orthostasis in POTS patients, increasing oscillatory CBF has been shown to be associated with memory deterioration and reduced neurovascular coupling. (82)

While the above studies have elegantly highlighted the complexities of cerebral hemodynamic response during orthostatic stress in relation to cognitive function in individuals with POTS, the extent to which these findings could be attributable to chronic fatigue syndrome is not known. (160) 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 POTS individuals encounter cognitive difficulties even when recumbent. (161) In a recent study, we found short-term memory and alertness were impaired in POTS patients whilst seated, despite demonstrating similar CBFv response to transient visual stimuli in the posterior cerebral artery

when compared with healthy controls. (11) 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 as compared to 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. (161)

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. (171) Nevertheless, TCD measures of CBF may be used as an objective tool to quantitate physiologic states in relation to objective cognitive and psychological assessments in clinical practice. (10) Whether reduced CBF 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 blood pressure. (172) We measured CBFv to the dominant cerebral hemisphere. While there is evidence that CBF is comparable between hemispheres during orthostatic stress,(83) CBF may vary between hemispheres during cognitive tasks. (173)

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. The use of fludrocortisone and rate control agents in some of the POTS group may have prevented the increase in heart rate with orthostatic stress and altered CBF responses to cognitive stress. However, withholding these agents could result in rebound tachycardia and exacerbation of symptoms that could modify CBF dynamics in response to prolonged cognitive and orthostatic stress.

Conclusions

Reduced cerebral blood flow and cognitive dysfunction were evident in POTS patients 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.

Chapter 5: Effect of Midodrine on Cognition and Cerebral Blood Flow in Postural Orthostatic Tachycardia Syndrome

Contextual Statement

In this chapter the effect of midodrine on symptom, cognition and CBFv are described. Patients who reported a reduction in their symptoms following administration of midodrine were selected for this study in order to determine if symptomatic improvement was accompanied by improved CBF dynamics during orthostatic or cognitive stress. Although we detected some improvement in cognitive performance following the administration of midodrine, we were unable to associate this symptomatic improvement with a change in CBFv response to cognitive stress.

There are several reasons why we may have missed a true association. Firstly, the period that elapsed to ensure the administered midodrine was absorbed and active resulted in a period during which some recovery from the baseline cognitive stress could occur. Therefore the repeat measure of CBFv when the cognitive protocol was repeated after the midodrine, whilst performed in patients who were fatigued from the previous cognitive and orthostatic stress, was not directly comparable to the prolonged cognitive stress in the protocol described in chapter 4 in which there was no rest period between repeated measures of RT and RVIP. Secondly, during the period midodrine was being absorbed, disturbance of the probe position resulted in deterioration in the quality of the TCD signal acquired from the MCA in some of the patients. Adjustment to improve the quality of the signal prior to the post midodrine baseline meant that there may have been some difference

in angle of insonance in the MCA during the post midodrine phase of the study when compared with the pre-midodrine phase of the study. The value of CBFv is highly dependent on the angle of insonance in the blood vessel. Thus, it is the change in CBFv from the baseline that is used to determine the impact of cognitive challenge on CBFv however we cannot say for sure that the baseline from which this change was measured was not itself altered by the administration of midodrine. Design of future studies may overcome these issues by continuing the cognitive stress throughout the period of drug absorption or by comparing the CBFv responses to CBFv responses in patients receiving placebo.

Introduction

Postural tachycardia syndrome (POTS) is characterized by a sustained increment in heart rate of greater than 30 bpm within 10 minutes of standing and in the absence of postural hypotension that improve on adopting a recumbent posture over at least 6 months duration. (164) Patients with POTS often describe significant limitations in their ability to work or study as a result of fatigue and cognitive dysfunction, often described as “brain-fog”. (161) Our previous work (Chapter 4) demonstrated a significant fall in cerebral blood flow velocity (CBFv) of POTS participants following prolonged cognitive stress. This suggests the cognitive dysfunction described by patients with POTS may reflect an inability to maintain adequate CBF to match the increased cerebral metabolic demands of prolonged cognitive activity.

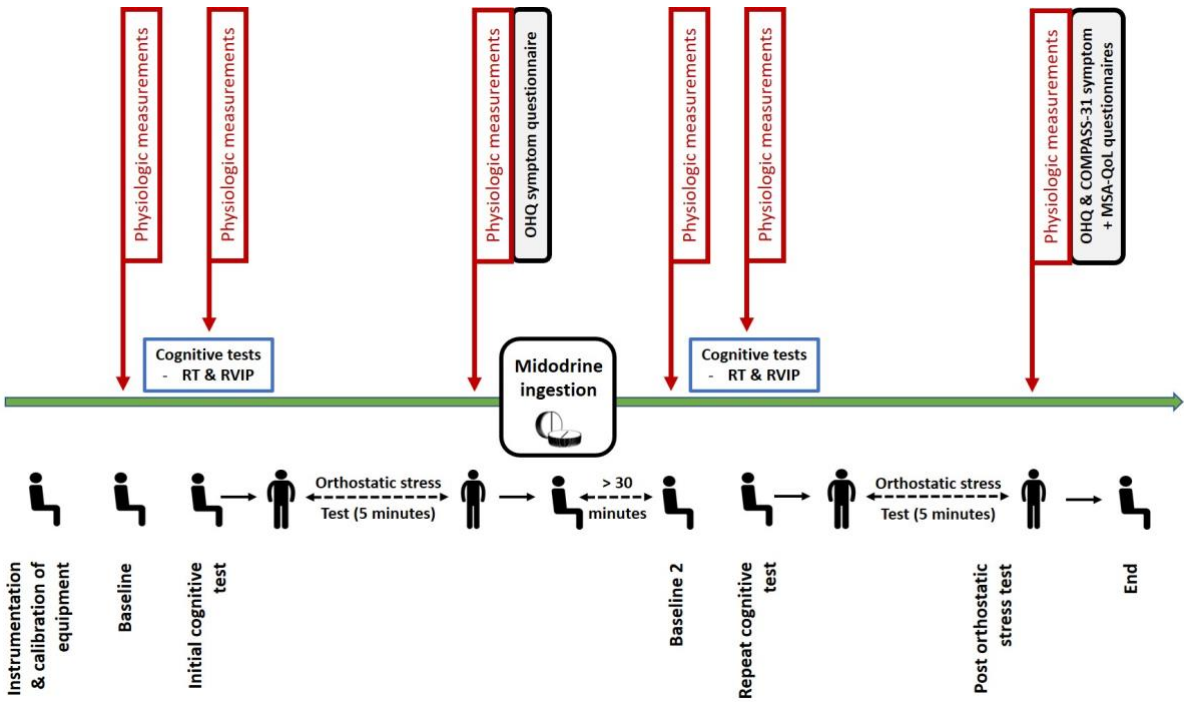
Management of POTS includes a variety of lifestyle measures and pharmacological agents targeted at reducing heart rate, increasing exercise tolerance, intravascular volume and vascular tone that have been shown to achieve only moderate efficacy. (109) Specifically,

midodrine is thought to increase vascular resistance directly through activation of peripheral adrenergic receptors. (174) It does not cross the blood brain barrier but may be effective in the sub-group of POTS patients in whom venous pooling in peripheral or splanchnic circulations can result in reduced venous return. (13),(138) Its efficacy in POTS was estimated at 65% with data stemming primarily from limited studies in paediatric patients. (9) However, the effect of midodrine on physiologic measures remain lacking with some data showing reduced heart rate increment on orthostatic stress, no changes in resting systemic blood pressure levels but no data on CBF. (23),(139) Here, we hypothesized that midodrine improves cognitive performance and augments CBF response to orthostatic and cognitive stress, and that this may underscore its effectiveness in patients with POTS.

Methods

We evaluated cognitive and hemodynamic responses (cardiovascular and cerebral) before and after midodrine (a highly bioavailable product with a peak plasma concentration of the prodrug and its metabolites between 30 to 60 minutes) administration in consecutively enrolled participants with POTS who provided written informed consent for this study. All physiologic measurements and cognitive assessments were undertaken at baseline during rest and during cognitive testing whilst seated as well as with 5-minute standing test (orthostatic stress). These measurements were repeated at least 30 minutes after ingestion of midodrine (Figure 1). This study was approved by the institutional human research ethics committee and conformed to the Declaration of Helsinki.

Figure 1: Study Protocol



Sequence of physiologic and cognitive measurements during the entire study protocol.

RT: reaction time, RVIP: rapid visual information processing, OHQ: orthostatic hypotension questionnaire,

COMPASS-31: Composite Autonomic Symptom Score-31, MSA-QoL: Multiple System Atrophy-Quality of Life.

Study eligibility and enrolment

POTS individuals 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 heart rate of >30 bpm during HUT or within 10 minutes of standing, without a postural blood

pressure drop of >20 mmHg. These symptoms included light-headedness, headache, fatigue, neurocognitive deficits, palpitations, nausea, altered vision, shortness of breath, or sensation of heat while upright, with no other medical explanation for the symptoms. All POTS patients were on treatment in accordance with current guidelines. Participants were included in this study if they were taking midodrine for treatment of POTS. (109) There were no exclusion criteria.

Patient preparation

All testing sessions were performed in the morning, with patients abstaining from alcohol and caffeine over the preceding 24 hours. All patients had been on stable medical therapy for POTS with no medication changes during the preceding month. Participants were permitted to continue all their usual medications except for vasopressors. Their usual morning dose of midodrine (α-adrenergic agonist, half-life of 3 hours) was withheld on the day of 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 interpretation of the study results. The study protocol was performed in a climate-controlled facility (22°C), with participants seated at a desk, emulating normal (school or clerical) working conditions.

Study protocol

Physiologic measurements included electrocardiogram (ECG), heart rate (HR), blood pressure (BP), respiratory rate and end-tidal carbon dioxide ($ETCO_2$). A single-lead ECG (FE132 Bioamp, ADInstruments Pty Ltd, Sydney, Australia) was placed for continuous ECG monitoring. Continuous, non-invasive 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. $ETCO_2$ was measured (Capnostream 20P, Medtronic, Minneapolis, MN, USA) via nasal prongs with mouth scoop (Smart CapnoLine Plus, Microstream, Medtronic). Data were exported to MATLAB (MathWorks, Natick, USA) for analysis.

We used transcranial doppler (TCD) to measure CBFv from the middle cerebral artery (MCA) of the dominant hemisphere (Doppler-BoxX, Compumedics DWL, Singen, Germany). A 2-MHz transducer probe (sample rate 100 Hz, PW, Compumedics DWL) was positioned with an adjustable headset (DiaMon, Compumedics DWL) on the subject's temporal bone (transtemporal window) to minimize movement of the probe during the study protocol. The envelope of the CBFv Doppler wave and all other physiologic measurements were simultaneously recorded with a data acquisition device (PL35/16; Powerlab, ADInstruments) and exported to MATLAB (MathWorks, Natick, MA, USA) for data analysis.

We performed cognitive testing using an iPad-based (Apple Inc, Cupertino, CA, USA) software collection tool (Cambridge Neuropsychological Test Automated Battery; CANTAB® 2019 version, Cambridge Cognition, Cambridge, UK). Specifically, we assessed the cognitive domains of attention and psychomotor speed by measuring rapid visual information processing (RVIP) reaction time (RT). The RT test provides an assessment of both the speed of motor and mental response. Here, we measured the time taken to release an on-screen button in response to a programmed visual stimulus. The RVIP test provides a measure of

sustained attention. The test assesses the ability and speed of the subject 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. Here, we measured the number of correct responses within 8 minutes.

Lastly, all participants completed the MSA-QoL (Quality of life assessment in Multiple System Atrophy) questionnaires to assess baseline quality of life measures. (168) Although not specifically designed for POTS, it has been well validated as a patient reported outcomes tool. Autonomic symptoms at baseline were assessed using the well validated, abbreviated Composite Autonomic Symptom Score (COMPASS- 31). (47) Further, in order to assess acute changes in symptoms with midodrine, we asked participants to rate their orthostatic symptoms taken from the Orthostatic Hypotension Questionnaire (OHQ). (49) The symptoms we 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 OHQ refers to symptoms experienced over the preceding week, we adapted it to assess immediate symptoms.

Statistical analysis

Continuous variables were presented as mean ± standard deviation while categorical variables were expressed as numbers and percentages. Non-normally distributed data were expressed as median and interquartile range (Q1, Q3). We used averaged physiologic data over 30 seconds at the following time points for comparison: at baseline whilst seated and >30 minutes after midodrine ingestion, whilst undertaking the cognitive tasks at before and

>30 minutes after midodrine ingestion in the seated position, and during the 5-minute stand test before and >30minutes after midodrine ingestion. A mixed effects model was used to assess intervention (baseline vs. midodrine) and condition (during cognitive testing and during orthostatic stress) as main effects and interaction between intervention and condition. Individual patient was modeled as random effect to account for repeated measures within individuals following midodrine ingestion. 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

Ten participants were enrolled with a mean age of 24±8 years. The majority of participants were female (n=9, 90%), all of whom were taking midodrine 2.5-10mg [median 5mg (IQR: 5, 10)] three times daily on a regular basis. Medication usage (aside from midodrine) are shown in Table 5.1. Self-reported symptom severity and quality of life scores (Table 1) demonstrate poor quality of life [(overall MSA-QoL 49 (32, 57)] and significant autonomic symptoms at baseline [COMPASS-31; 28 (39, 59)].

Table 5.1: Patient characteristics

Patient characteristics	
Age, yrs	24 ± 8
Female, n (%)	9 (90)
Medications, n (%) □ Fludrocortisone □ Ivabradine □ Propranolol	 3 (30) 2 (20) 1 (10)
Patient symptom scores: median (Q1, Q3)	
MSA-QoL	49 (32, 57)
COMPASS-31	28 (39, 59)

Legend Table 5.1: Patient characteristics

POTS: postural tachycardia syndrome, BP: blood pressure, $ETCO_2$: end-tidal carbon dioxide, CBFv: cerebral blood flow velocity, COMPASS-31: Composite Autonomic Symptom Score-31, MSA-QoL: Multiple System Atrophy-Quality of Life.

The COMPASS-31 (adjusted) score is a validated score calculated from the raw COMPASS-31 score after applying a weighting that takes into account the number of points and relative importance of organ systems to the assessment of autonomic dysfunction. (47) A high score indicates greater severity of symptoms related to autonomic dysfunction. The MSA-QoL score assesses factors that impact on quality of life with a high score indicating significant impairment in quality of life. (168)

Physiologic and cognitive measurements during cognitive testing pre- and post-midodrine

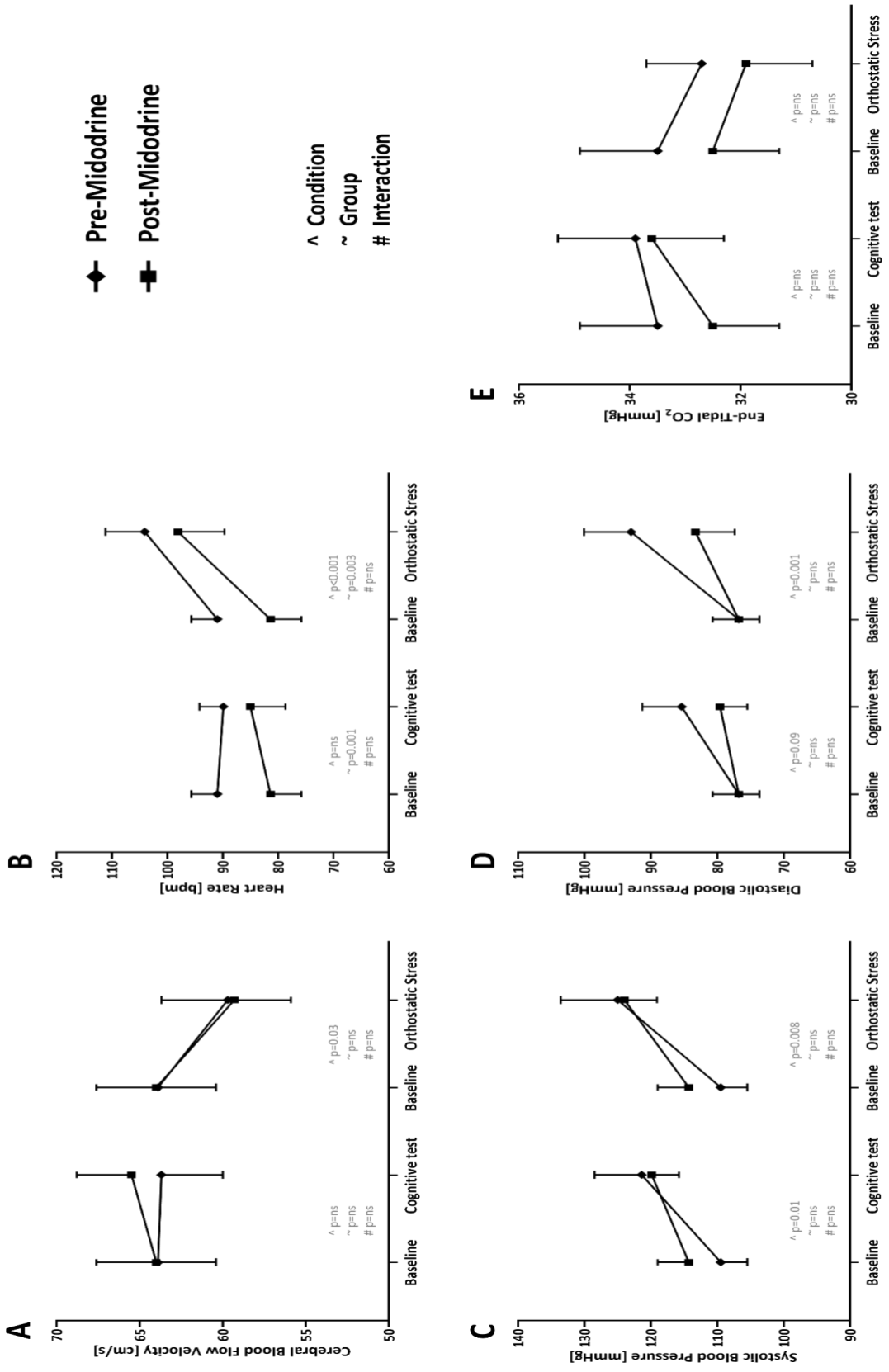
Mean HR was consistently slower post-midodrine (p=0.001) although no significant changes were seen with cognitive testing, and midodrine did not impact on HR with cognitive testing (p=0.2, Table 5.2 & Figure 5.2B). Systolic BP increased (p=0.01) and diastolic BP showed an upward trend with cognitive testing (p=0.09), but midodrine did not affect either systolic or diastolic BP nor did it impact on the degree of increase in both systolic and diastolic BP with cognitive testing (both p=0.4, Table 5.2, Figure 5.2C & D). There were no changes in $ETCO_2$ and CBFv with cognitive testing while midodrine use did not impact on both parameters and its changes with cognitive testing (both p>0.6, Table 5.2, Figure 5.2A & E). Cognitive testing demonstrated improved reaction time following the administration of midodrine (398±22 vs. 431±34ms, p=0.002) although the number of correct responses with RVIP test did not change (p=0.15, Table 5.2).

Table 5.2: Physiologic and cognitive measurements during cognitive testing pre- and post-midodrine

	POTS (n=10) Pre-midodrine		**POTS (n=10) Post-midodrine**		**P value**
	Baseline	**cognitive testing**	**Baseline**	**cognitive testing**	
CBFv (cm/s)	63.9±11.1	63.7±11.7	64.0±11.4	65.5±10.6	0.6
Heart rate (*bpm*)	91±15	90±14	81±18	85±20	0.2
Systolic BP (*mmHg*)	110±13	121±23	114±15	120±13	0.4
Diastolic BP (*mmHg*)	77±10	85±19	77±12	80±13	0.4
$ETCO_2$ (*mmHg*)	34±5	34±5	33±4	34±4	0.7
RVIP (*no. correct responses*)	-	34±9	-	39±12	0.16
Reaction time (*ms*)	-	431±34	-	398±22	0.002

P value denotes comparison between pre-midodrine and post-midodrine response to cognitive stress, POTS: postural tachycardia syndrome, CBFv: cerebral blood flow velocity, BP: blood pressure, $ETCO_2$: end-tidal carbon dioxide, RVIP: rapid visual information processing, no.: number. Data are presented as mean ± standard deviation or median (Q1, Q3). OHSA: Orthostatic Hypotension Symptom Assessment, OHQ: Orthostatic Hypotension Questionnaire. OHSA is the symptom assessment component of the OHQ questionnaire used to quantify symptoms present at the time the questionnaire was completed.(49) Six symptoms are given a score from 0 (symptom not present) to 10 (most severe), with a maximum total score of 60.

Figure 5.2: Physiologic measurements pre- and post-midodrine with cognitive test & orthostatic stress



Legend Figure 5.2: Physiologic measurements pre- and post-midodrine with cognitive test & orthostatic stress

The p values in each graph denote comparisons for ^condition (baseline vs. cognitive test or baseline vs. orthostatic stress) in both groups, ~group (pre- vs. post-midodrine) and #interaction (between condition and group). For ease of illustration, all values plotted are mean ± standard error of the mean with uni-directional error bars

Physiologic measurements during orthostatic stress pre- and post-midodrine

Orthostatic stress resulted in reduced CBFv ($p=0.03$, Figure 2A), increased HR ($p<0.001$, Figure 2B), systolic ($p=0.008$, Figure 5.2C) and diastolic BP ($p=0.001$, Figure 5.2D) while ETCO2 remained unchanged ($p=0.3$, Figure 5.2E). Mean HR was consistently lower while all other physiologic parameters (including CBFv) remain unchanged post-midodrine. Further, midodrine had no impact on the degree of change in all physiologic parameters with orthostatic stress (all $p>0.3$, Table 5.3).

Table 5.3: Physiologic changes with 5-minute orthostatic stress pre- and post- midodrine

	POTS (n=10) Pre-midodrine		**POTS (n=10) Post-midodrine**		**P value**
	Baseline	**Post orthostatic stress**	**Baseline**	**Post orthostatic stress**	
CBFv *(cm/s)*	63.9±11.1	59.7±11.9	64.0±11.4	59.3±10.3	0.7
Heart rate (bpm)	91±15	104±21	81±18	96±25	0.4
Systolic BP (*mmHg*)	110±13	125± 26	114±15	124±15	0.6
Diastolic BP (*mmHg*)	77±10	93±21	77±12	90±18	0.6
$ETCO_2$ (*mmHg*)	34±5	33±3	33±4	32±4	1.0

P value denotes comparison between pre- and post-midodrine from baseline to post orthostatic stress. POTS: postural tachycardia syndrome, CBFv: cerebral blood flow velocity, BP: blood pressure, $ETCO_2$: end-tidal carbon dioxide. All data are presented as mean ± standard deviation.

Orthostatic symptom assessment

Following the administration of midodrine, orthostatic symptoms score from OHQ improved significantly [36 (IQR: 26, 38) vs. 23 (11, 24); p <0.001].

Discussion

In this study, comprehensive physiologic measurements in patients with POTS showed that midodrine exerted a consistent HR lowering effect while orthostatic stress resulted in significant increase in blood pressure and HR. We did not demonstrate significant changes in physiologic parameters attributable to midodrine administration when the POTS patients were subjected to cognitive testing or orthostatic stress. Despite the lack of impact on CBFv within 1 hour of midodrine administration, there was an improvement in patient reported orthostatic symptoms as well as improved psychomotor speed.

The POTS patients in our study reported a significant symptom burden and reduced quality of life consistent with previous studies. (175) Improvement in symptoms has been reported previously in POTS patients following regular midodrine therapy,(176) and during head-up tilt test following a single dose of midodrine,(54) however objective physiologic evidence for the use of midodrine in the management of POTS is limited. (9) Individual studies have shown that midodrine use conferred blood pressure increase in hypotensive cohorts with idiopathic hypotension, spinal cord injury, and neurogenic hypotension, (177),(178, 179) but a meta-analysis of all studies in which the effect of midodrine on blood pressure was studied in hypotensive cohorts did not find a statistically significant effect on BP following the

administration of midodrine(180) and no effect on BP was noted following midodrine administration in a normotensive control group during a study of individuals with spinal cord injury and able bodied controls. (181) In POTS patients, the effects of midodrine include reduced heart rate increment on orthostatic stress and no changes in resting systemic blood pressure levels. (23),(139) Our data affirms the heart rate lowering effect of midodrine in POTS that has been previously reported. Studies measuring the effect of midodrine on CBFv response to cognitive activation have generated conflicting results. In a group of patients with spinal cord injury, and in a control group, midodrine did not alter the CBFv response to a serial subtraction task. (181) Others have reported that midodrine resulted in a greater increment in CBFv to a brief RT task than was seen following placebo in patients with chronic hypotension. (177) This study provides new information on midodrine use in patients with POTS where there is a lack of impact on CBFv whilst undertaking cognitive testing and with 5 minutes of orthostatic stress within 1 hour of dosing.

An increase in regional CBFv generally accompanies cognitive activation, with increased delivery of oxygen and nutrients to the metabolically active cells. (182),(183) Others have associated hypotension with a reduced capacity to increase CBF in response to a reaction task,(177) and lower CBFv during a working memory task. (182) Our subjects' BP was higher during cognitive testing and it remains unclear why the increase in CBFv was not observed in our POTS patients. At the same time, it is unlikely that the cognitive improvements can be explained by the HR lowering effect of midodrine alone. It is possible that either the midodrine dose administered was insufficient or the effect of midodrine on CBFv was longer than the window we anticipated.

Study limitations

This study has small sample size which could have contributed to some of the negative findings. However, in the absence of published data on the impact of midodrine on CBFv, statistical powering could not be undertaken. TCD measures CBF velocity, as opposed to CBF. The measures are only equivalent if the vessel diameter does not vary. We did not assess MCA diameter during the study, but others have previously observed only minor changes (<4%) in diameter of the MCA in response to hypocapnia and changes in BP. (172) We measured CBFv in the MCA from the dominant cerebral hemisphere only. While there is some evidence that CBF may be comparable between hemispheres during orthostatic stress,(83) CBF may vary between hemispheres during cognitive testing. (173),(184) Without a placebo controlled arm, it is not possible to attribute improvement in symptoms and cognitive function to midodrine alone. Repeated physiologic measurements at additional time-points might have provided us with further insights on the potential effect of midodrine on cerebral perfusion. The use of fludrocortisone and HR lowering agents may have altered our patients' CBF and systemic hemodynamic responses to cognitive and orthostatic stress. However, withholding these agents could also result in rebound tachycardia and exacerbation of symptoms that may impact on various physiologic parameters. It remains unclear whether the physiologic impact of midodrine would differ in different POTS subtypes with peripheral venous pooling or low blood volume. (64)

Conclusion

Acute administration of midodrine in POTS resulted in improved orthostatic symptoms and cognitive function despite a lack of impact on cerebral perfusion during cognitive testing and orthostatic stress within the first hour. Further studies are needed to further delineate the mechanisms responsible for the symptomatic benefits with its use.

Chapter 6: Plasma Exchange Therapy in Postural Tachycardia Syndrome: A Novel Long-term Approach?

Statement of Authorship for: Plasma Exchange Therapy in Postural Tachycardia Syndrome: A Novel Long-term Approach?

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Chapter 6: Plasma exchange

Contextual statement

In Chapter 1 the heterogeneity in the pathophysiological underpinnings of POTS was described, along with the results of a number of studies in which the presence of autoantibodies had been detected in the plasma of patients with POTS. (185),(129) Although plasma exchange is traditionally utilised in the treatment of patients with an identified antibody, the process of plasma exchange does not require the identification of the causative antibody (in contrast to therapeutic approaches involving absorption or neutralisation of antibodies). When there is suspicion that an auto-antibody may be driving the pathologic process, there may be value in exchanging plasma with albumin in order to assess symptomatic response following removal of pathologic autoantibodies. In this manuscript we describe this approach in a patient with POTS.

In this case, the patient described symptomatic improvement following an initial 2 week period, involving 5 discrete episodes of plasma exchange, despite a greater increment in HR in response to orthostatic challenge performed after plasma exchange. Since symptom severity is not necessarily correlated with HR in patients with POTS, and HR response to orthostatic stress may vary from day to day, we did not exclude the possibility that plasma exchange had removed a pathologic autoantibody. However we had no objective biological measure to validate the subjective improvement in patient symptom scores. After a poor response to alternative therapeutic approaches (including repeated infusion of normal saline and a 6 month trial of azathioprine), a multi- disciplinary team agreed to a further period of therapeutic plasma exchange for this patient. We studied CBFv responses to orthostatic and cognitive stress in this patient to determine if there might be a correlation between this

objective measure and her symptom score. In the case report below, we describe the results of CBFv responses to orthostatic and cognitive stress performed approximately 12 months after the patient had commenced maintenance therapeutic plasma exchange at approximately monthly intervals. The baseline measures were assessed on the day prior to one of her plasma exchange treatments, and the post treatment assessment was performed 3 days after the plasma exchange therapy. The timing of the post treatment assessments was based on the patient's experience that day 3 post plasma exchange was usually when symptomatic response was maximal, as the process of plasma exchange itself often resulted in fatigue for several days.

In total, five patients with symptoms associated with POTS have undergone plasma exchange at the Royal Adelaide Hospital. In each case, induction plasma exchange was offered after informed consent was given. The approach consisted of 5 cycles of plasma exchange over a period of 2 weeks. Two patients did not describe a significant improvement in symptoms or hemodynamic parameters following the induction therapy and no further plasma exchange was undertaken. In addition to the case reported below, 2 other young women resistant to or intolerant of the usual therapeutic modalities for POTS reported improvement following induction plasma exchange therapy. A period of maintenance plasma exchange therapy was provided for these 2 patients, however infection of the intravascular device in one patient, and the short duration (less than 2 weeks) of benefit following each session in both patients, lead to a decision to abandon this approach in both patients. Overall, our experience with plasma exchange therapy in patients with POTS has been disappointing.

Case report:

A 32 year-old female developed severe orthostatic intolerance associated with fatigue and cognitive difficulties following an episode of shingles in 2015. She had pre-existing medical co-morbidities of Crohn's disease, joint hypermobility, gastroesophageal reflux and narcolepsy. Standing test resulted in light-headedness with acrocyanosis of her extremities within 5 minutes and significant heart rate increase from 77 to 110 bpm without any blood pressure drop, indicative of POTS. Routine blood investigations were largely unremarkable. Autoimmune assays, immunoglobulins, complement and plasma noradrenaline levels were also normal. Her symptoms of presyncope, palpitations, nausea, headache, fatigue and exercise intolerance were refractory to standard interventions including increasing salt and water intake, fludrocortisone and propranolol over a 12-month period.

A trial of plasma exchange as immunomodulatory therapy was undertaken with informed consent, involving exchange of 3 litres of plasma with 4% albumin over 2-4 hours on six occasions over a 2-week period. Her symptom improvement following plasma exchange was assessed with questionnaires (Table 6.1): almost 40% improvement in The Composite Autonomic Symptom Score (COMPASS 31) (benefits seen in several domains); 38% improvement in orthostatic hypotension symptom assessment (OHSA) score; and 29% improvement in orthostatic hypotension daily activity scale (OHDAS) (Table 6.1). Further, neuropsychological assessment with CANTAB (Cambridge neuropsychological test automated battery) showed slight improvement in attention, alertness and memory (Table 6.1). However,

there was no improvement in biological parameters during a 10-minute tilt-table test performed 3 days after completion of the 2-week plasma exchange (Table 6.1).

The patient's symptoms returned 4 weeks after cessation of plasma exchange. Over the subsequent 5 months, there was no improvement in symptoms despite regular intravenous normal saline infusions and oral azathioprine. Eventually maintenance plasma exchange was recommenced at two to four weekly intervals. Reassessment of symptom scores, and responses to orthostatic and cognitive assessment after approximately 12 months of therapy are reported in Table 6.1 (far right column). Improved positional hemodynamics including cerebral blood flow after cognitive challenge (CANTAB: rapid visual information processing test) at three days after versus one day prior to plasma exchange (Figure 6.1). Our patient's positive response to plasma exchange remains durable with maintenance plasma exchange sessions for more than 18 months through peripheral intravenous cannula with no adverse events.

Discussion

Others have reported favourable outcomes of plasma exchange in immune mediated conditions such as autoimmune autonomic ganglionopathy, Guillain-Barré syndrome, myasthenia gravis and idiopathic thrombotic thrombocytopenic purpura. We posit that the removal of auto-antibodies may underscore the beneficial effects of plasma exchange in POTS. There has been one other report of shorter term immunomodulatory therapy involving prednisolone and plasmapheresis in a patient who developed POTS after human papillomavirus vaccination. (186) The technique of plasma exchange is considered to be of

sufficiently low risk with extensive experience to date in healthy donors and without any risk of serious or fatal consequences from conventional immunomodulating agents. The positive outcome of our case with long-term plasma exchange calls for further studies to define the immune-based mechanisms that may be responsible for this chronic debilitating condition.

Table 6.1: Response to acute and chronic plasma exchange in a patient with POTS

	Before plasma exchange	After plasma exchange	Percentage improvement	Chronic maintenance plasma exchange
[A] Symptom Questionnaires				
COMPASS 31: Composite Autonomic Symptom Score				
- Orthostatic intolerance	8	5		4
- Vasomotor	5	3		3
- Secretomotor	0	0		0
- Gastrointestinal	17	13		10
- Bladder	3	2		4
- Pupillomotor	11	4		4
Total (raw)	44	28	36%	25
Total (weighted)	**60**	**38**	**37%**	**33**
OHQ: Orthostatic Hypotension Questionnaire				
- OHSA (Orthostatic Hypotension Symptom Assessment)	47	29	**38%**	22
- OHDAS (Orthostatic Hypotension Daily Activity Scale)	31	22	**29%**	24
[B] Cognitive Assessment				
CANTAB: Cambridge Neuropsychological Test Automated Battery				
- Reaction time (s)	402	366	**9%**	375
- Rapid visual information processing latency (ms)	467	466	**0%**	424
- Attention switching task latency (ms)	931	755	**19%**	552
- Delayed matching to sample response latency (ms)	3900	2831	**27%**	2986
[C] Hemodynamics Parameters				
10-minute tilt table test				
- Baseline heart rate (bpm)	81	86	**-6%**	-
- Maximum heart rate (bpm)	104	114	**-10%**	-
- Baseline systolic blood pressure (mmHg)	125	133	**6%**	-

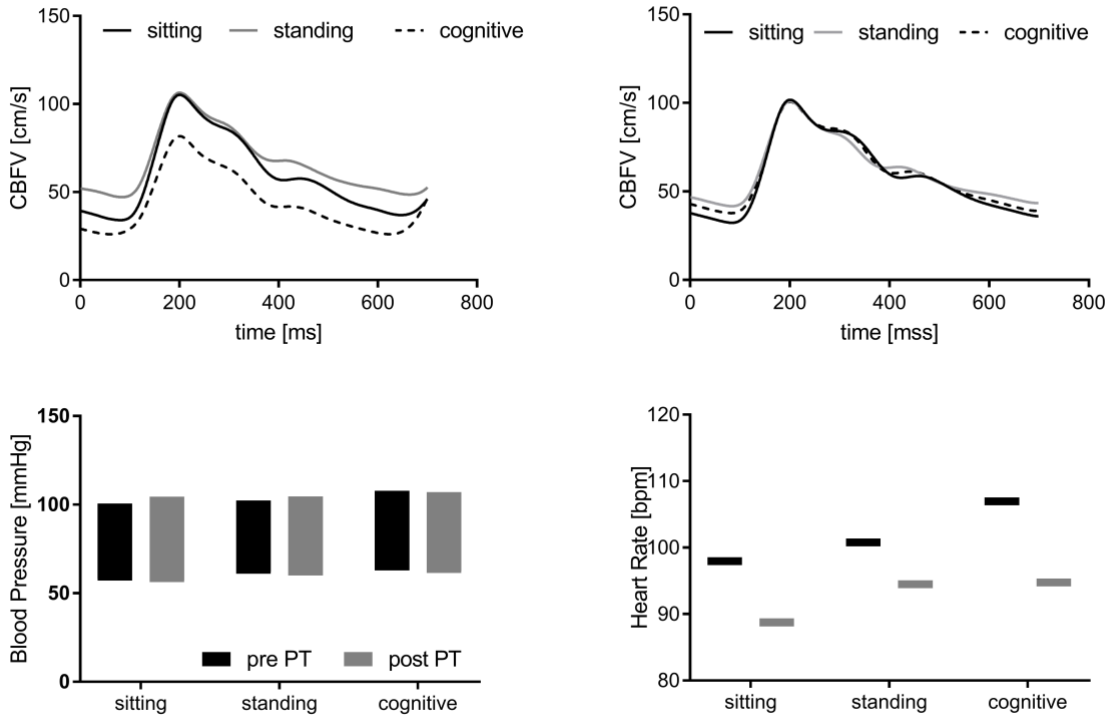

Figure 6.1: Hemodynamic and cerebral blood flow changes in a patient treated with chronic plasma exchange therapy

The attenuation in cerebral blood flow velocity profile with cognitive challenge (top left) was ameliorated following plasma exchange (top right). Pulse pressure (shaded bars, bottom left) was marginally higher after plasma exchange whilst seated, standing and with cognitive challenge. Heart rate (bottom right) was consistently lower after plasma exchange, despite increment with both standing and cognitive challenge.

Conclusion

The utility of measuring CBFv response to orthostatic and cognitive challenge in patients with POTS requires further validation, however in this case the improvement in CBFv response to cognitive stress appeared to correlate with symptomatic response.

Thesis Conclusion:

During the course of this work, I highlighted the paucity of evidence for the current treatment modalities utilised in the management of patients with POTS. The heterogeneity of the underlying pathophysiology driving the physiological changes in POTS was highlighted and the need for an objective measure of treatment response was emphasized. Recognizing the subjectivity of symptom questionnaires and the discordance of symptom severity and HR control in this patient group, the value of TCD as an objective measure of CBFv during orthostatic and prolonged cognitive assessment was studied.

Firstly, in chapter 3 I describe the results of a pilot study in which the use of a portable ultrasound machine was used to measure responses in CBFv to a brief visual stimulus in patients with POTS and healthy controls. During this study, cognitive assessment was also undertaken. This is followed, in Chapter 4, by the description of a larger study in which headgear fixation of a probe and a physiological laboratory setup allowed for recording of hemodynamic and CBFv recording during orthostatic and prolonged cognitive stress in POTS patients and healthy controls.

Although the POTS group had slower reaction times and lower accuracy in cognitive challenges in this study, we found similar responses to those seen in the control group in both hemodynamic and CBFv responses to a 5 minute stand test and to a brief cognitive challenge. A difference emerged between healthy controls and patients with POTS when cognitive challenge

was prolonged, however, with a greater decline in CBFv relative to the earlier cognitive assessment seen in the POTS group. The increase in symptoms from baseline to the end of this study was significantly greater in the POTS group.

Many patients with POTS describe significant symptomatic improvement with midodrine therapy. Thus, in chapter 5 there follows a description of my work in which I explored the hypothesis that vasopressor therapy might be exerting some effect on CBFv response to cognitive stress, despite the fact that it does not cross the blood brain barrier. The study involved TCD measures of CBFv responses to cognitive and orthostatic stress both before and after the administration of midodrine. No evidence for change in CBFv in response to either orthostatic or cognitive stress following administration of midodrine was detected despite the reduction in symptoms and improvement in reaction time seen when the cognitive assessments was repeated following the administration of midodrine. It is possible this negative finding reflects the small number of patients in the study or technical issues with the study design. The significant improvement in reaction time in the assessment performed after the administration of midodrine suggests that, unfortunately, the sensitivity of TCD as a measure of CBFv response to orthostatic and cognitive stress may not be adequate to utilise as an endpoint in clinical trials.

In Chapter 6 I have described the use of TCD to monitor the effect of a novel therapeutic intervention, plasma exchange, on CBFv in a patient with POTS. Plasma exchange has been used in various conditions in which the presence of antibodies directed against endogenous antigens

are thought to play a critical role. Generally, conditions in which plasma exchange therapy is a recognized therapeutic approach an assay for the causative auto-antibody is available. This is not the case in POTS, despite reports of antibodies targeting adrenergic, cholinergic or cardiac lipid proteins present in the plasma of patients with POTS. The potential for immunotherapy is therefore appealing but carries with it significant risk of adverse events. In our patient, symptomatic improvement was associated with a reduction of HR increment to both orthostatic and cognitive stress, and a suggestion that CBFv was improved during cognitive assessment following plasma exchange when compared to the CBFv response during cognitive assessment prior to plasma exchange.

Overall, our studies of CBFv responses to orthostatic and cognitive challenges, whilst providing some indication that CBFv may deteriorate with prolonged cognitive stress in patients with POTS, did not correlate well with symptom severity. Whilst TCD is a useful tool to study the changes in CBFv associated with brainfog, a search for alternative biologic assays are needed to support the future assessment of novel therapeutic interventions in the management of POTS.

Future directions for study

Until a biomarker is identified which provides a meaningful correlation between symptom severity and pathophysiology in patients with POTS, interpretation of therapeutic efficacy for novel treatment approaches will require large placebo-controlled, randomised clinical trials to compensate for the impact of the significant placebo effect associated with interventions in this patient population. Developments in the fields of genetics and immunology

provide some hope in the future for diagnostic and therapeutic options for patients with POTS. Whilst plasma exchange therapy in patients with POTS seems unlikely to play a great role, the demonstration of auto-antibodies with adrenergic activity in plasma collected from patients with POTS suggests that, in some patients, immune-mediated approaches may yet have a role. Not covered in detail in this thesis but noted as a potential future direction of research is the exploration of the role of NET activity, and with it, the possibility of intervening in NET function.

The high prevalence of “brainfog” in patients with POTS, however, makes CBF an area that warrants further research. An alternative technique to measure regional CBF, such as functional magnetic resonance imaging (fMRI), may prove valuable in these patients. Although tilt tests and prolonged cognitive protocols are impractical when studying CBF using fMRI, it may be possible to replicate many of the physiological changes associated with orthostatic stress through the use of lower body negative pressure.

Ultimately, the heterogeneity of the condition is a huge barrier to progress in our understanding of POTS. Progress in this condition may come only through piecemeal approaches, each applicable to only a small percentage of the patients with unique variations in physiological processes that ultimately result in a brisk heart rate response to orthostatic stress.

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