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# Postural orthostatic tachycardia syndrome is an under-recognized condition in chronic fatigue syndrome

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## Summary

**Background:** It has been suggested that postural orthostatic tachycardia syndrome (POTS) be considered in the differential diagnosis of those with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). Currently, measurement of haemodynamic response to standing is not recommended in the UK NICE CFS/ME guidelines.
**Objectives:** To determine prevalence of POTS in patients with CFS/ME.
**Design**: Observational cohort study.
**Methods:** Fifty-nine patients with CFS/ME (Fukuda criteria) and 52 age- and sex-matched controls underwent formal autonomic assessment in the cardiovascular laboratory with continuous heart rate and beat-to-beat blood pressure measurement (Task Force, CNSystems, Graz Austria). Haemodynamic responses to standing over 2 min were measured. POTS was defined as symptoms of orthostatic intolerance associated with an increase in heart rate from the supine to upright position of >30 beats per minute or to a heart rate of >120 beats per minute on standing.
**Results:** Maximum heart rate on standing was significantly higher in the CFS/ME group compared with controls ($106 \pm 20$ vs. $98 \pm 13$; $P = 0.02$). Of the CFS/ME group, 27% (16/59) had POTS compared with 9% (5) in the control population ($P = 0.006$). This difference was predominantly related to the increased proportion of those in the CFS/ME group whose heart rate increased to >120 beats per minute on standing ($P = 0.0002$). Increasing fatigue was associated with increase in heart rate ($P = 0.04$; $r^2 = 0.1$).
**Conclusions:** POTS is a frequent finding in patients with CFS/ME. We suggest that clinical evaluation of patients with CFS/ME should include response to standing. Studies are needed to determine the optimum intervention strategy to manage POTS in those with CFS/ME.



## Introduction

Epidemiological studies suggest that in the United Kingdom 0.2–2% of the population is affected by chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) that accounts for 1% of all primary care consultations.[1] CFS/ME affects all ages and can profoundly influence a sufferer's ability to function on a daily basis, work or attend school. Despite its impact on the population, the cause of CFS/ME remains unknown and there are no effective pharmacological treatments.

Studies show that fatigue is experienced by almost 50% of those with postural orthostatic tachycardia syndrome (POTS)[2] and it has been suggested that the presence of POTS should be considered in the

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differential diagnosis of all patients diagnosed with CFS/ME.[3,4] However, evaluation for POTS is not considered a routine part of the clinical evaluation of those with CFS/ME and the recently published UK NICE CFS/ME guidelines do not recommend measurement of haemodynamic responses to standing in the assessment of those diagnosed with CFS/ME.[5]

We therefore examined the prevalence of POTS in a cohort of those with CFS/ME. To do this, responses to standing were examined in a large series of subjects with CFS/ME compared with controls.

# Methods

## Subjects

Subjects with CFS/ME (Fukuda Criteria[6]) were identified via the patient support group 'ME North East'. Subjects had been diagnosed with CFS/ME in a specialist CFS/ME service within 2 years of assessment in the autonomic laboratory. Controls were recruited via notices placed within the hospital. Both patients and controls were excluded if taking any medication that could influence assessment of haemodynamics (e.g. β-blockers, calcium antagonists, anti-depressants). Subjects were excluded if not in sinus rhythm, unable to stand or unable to attend the autonomic laboratory for assessment. The study was reviewed and approved by the Newcastle and North Tyneside Local Research Ethics Committee. All patients and controls provided written informed consent.

## Symptom assessment tools

Subjects and controls completed on the day of assessment, a measure of fatigue impact [Fatigue Impact Scale (FIS)]. The FIS is a 40-item symptom-specific profile measure of health-related quality of life, commonly used in medical conditions in which fatigue is a prominent symptom. The scale allows patients to rate each item on a scale of 0–4, with 0 representing no problem and 4 representing an extreme problem. Individual scores are summed to provide a total score with higher scores indicating worse fatigue. This tool has been validated for self-completion (i.e. assesses a patient's perceived level and impact of fatigue) in both CFS/ME and normal populations.[7,8]

## Assessment of haemodynamic responses to standing

Subjects underwent formal autonomic assessment in the cardiovascular laboratory. All subjects refrained from smoking and caffeine ingestion on the day of investigation and ate a light breakfast only. All investigations were performed at the same time of day, and took place in a warm, quiet room. All cardiovascular assessments were carried out with continuous heart rate and beat-to-beat blood pressure measurement (Task Force, CNSystems). Heart rate and blood pressure responses to standing over 2 min were measured.[9] Data were digitized and stored for offline analysis by an investigator blinded to the fatigue status and whether data was from patients or controls. Baseline measurements were taken as an average for 20 beats in supine position immediately prior to standing. Orthostatic heart rate change was the change in mean heart rate from baseline on standing. The absolute maximum heart rate on standing was also recorded.

POTS was diagnosed using recognized diagnostic criteria[10] and was defined as symptoms of orthostatic intolerance associated with an increase in heart rate from the supine to upright position of $>30$ beats per minute (beat to beat) or to a heart rate of $>120$ beats per minute on immediate standing or during the 2 min of standing.

## Statistical analysis

All variables were parametric and therefore comparisons between groups and correlations were therefore made using the appropriate statistical tests. For continuous variables, comparisons were made using un-paired *t*-tests, whilst for categorical data comparisons were made using Fisher's exact test. Results are presented throughout as mean ± SD.

# Results

## Subjects

Sixty-three subjects with CFS/ME were identified via the patient support group 'ME North East'. One patient was found not to be in sinus rhythm, two patients were unable to stand without support, and one subject was too unwell to attend the autonomic laboratory for assessment. The study cohort therefore comprised 59 patients with CFS/ME (Fukuda criteria). Mean age of the CFS/ME group was $47 \pm 12$ years with 41 (69%) females. This group was compared with a group of 52 controls matched group-wise for age and sex [mean age $50 \pm 13$ years; $P = 0.3$; 34 (66%) females]. Predictably the CFS/ME group were significantly more fatigued compared with the control population (assessed using the FIS; $96 \pm 28$ vs. $13 \pm 21$, $P < 0.00001$).

**Table 1** Systolic blood pressure (SBP, mmHg) responses in the CFS/ME group compared with matched controls

| | CFS/ME | Controls | *P* |
|---|---|---|---|
| Baseline SBP | 130 ± 18 | 131 ± 21 | 0.7 |
| Nadir SBP | 112 ± 22 | 114 ± 24 | 0.7 |
| Change in SBP | 18 ± 11 | 17 ± 11 | 0.8 |

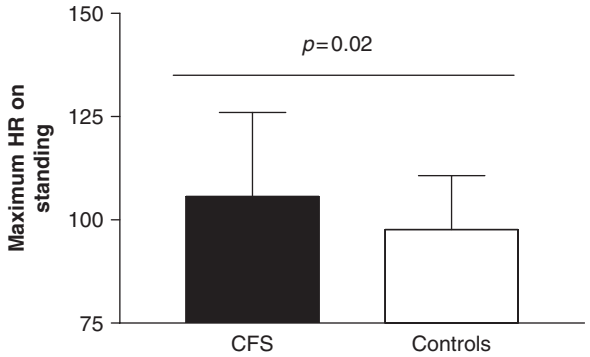


**Figure 1.** Maximum heart rate (HR) attained on standing was significantly higher in the CFS/ME group compared with controls. Results are presented as mean ± SD.

## Haemodynamic responses to standing in CFS/ME compared with controls

Although mean blood pressure responses to standing were lower in those with CFS/ME compared with controls none of these parameters reached statistical significance (Table 1).

When considering heart rate responses to standing, despite a baseline heart rate that was not significantly different between the CFS/ME group and controls (84 ± 17 vs. 80 ± 14; $P = 0.2$) the maximum heart rate attained on standing was however significantly higher in the CFS/ME group compared with controls (106 ± 20 vs. 98 ± 13; $P = 0.02$) (Figure 1).

## Prevalence of POTS in the CFS/ME group compared with controls

When the diagnostic criteria for POTS were applied to both the CFS/ME and control groups, 27% (16/59) of the CFS/ME group were found to have POTS, which was significantly higher than the 9% (5) found in the control population (Figure 2). This difference was predominantly related to the increased proportion of those in the CFS/ME group whose heart rate increased to above 120 beats per minute on standing.

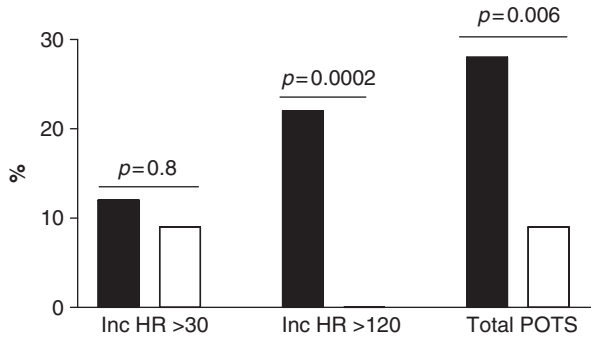


**Figure 2.** The proportion of the CFS/ME group (black bars) compared with controls (clear bars) who were found to have POTS.

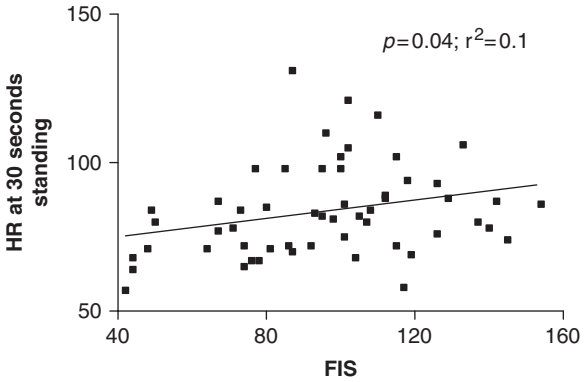


**Figure 3.** Increasing fatigue (FIS) was associated with the increase in heart rate (HR) 30 s after standing, in those with CFS/ME.

There were no significant differences in fatigue severity, age or sex between those found to have POTS compared with those CFS/ME patients who did not have POTS (data not shown).

Increasing fatigue was associated with the increase in heart rate 30 s after standing (Figure 3).

# Discussion

This study describes for the first time, the prevalence of POTS in a cohort of patients with the clinical diagnosis of CFS/ME. POTS is a frequent finding in our patients with CFS/ME and we would therefore suggest that the clinical evaluation of patients presenting with CFS/ME should include heart rate responses to standing. The prevalence of POTS may in fact be even higher in this patient group than that reported here, as we limited our observations of haemodynamics to 2 min of standing. Studies are needed in order to determine whether the prevalence may be even higher if monitoring is continued for longer periods.

Symptoms on standing are a frequently described symptom in those with fatigue in general[11,12] and CFS/ME in particular[12–21] and the physiological mechanisms that lead to these symptoms are poorly understood. The pathophysiology of POTS remains unclear, and includes autonomic abnormalities, hypovolaemia or low blood volume. Furthermore, whether management of POTS by normalization of heart rate, leads to improvements in fatigue and the other symptoms of CFS/ME requires further study. We would suggest, however, that our finding that higher levels of perceived fatigue were associated with the degree to which heart rate increases on standing, would imply that this offers potential opportunities for intervention. It is currently unclear whether POTS is a separate clinical entity distinct from CFS/ME or whether POTS is a particular subset of CFS/ME where a specific group of symptoms are particularly marked. Longitudinal clinical studies are needed in order to define this further. In the meantime, optimizing the management of those with POTS is critical. The largest series of patients in the literature confirm a significant symptom burden in those with POTS including weakness, muscle aches and pains.[2] In view of these findings and without evidence to the contrary, we would strongly suggest that current medication regimes for the management of POTS are simply symptomatic and need to be combined with the multifaceted effective interventions performed within the context of the CFS/ME clinical networks, thus incorporating into POTS management the other effective components of a fatigue management programme.[5] Studies are proposed within our group to compare the efficacy in POTS patients of medication alone compared with medication with conventional CFS/ME management.

Interestingly, our CFS/ME with POTS group differed from the demographic group reported in the largest series of POTS patients to date. In the Mayo series,[2] 86.8% were females whilst in our group this was lower at 69%, and our group did include 31% who were over the age of 50 years (mean age in the Mayo series was 30 years). In the Mayo series, only 48% of those with POTS experienced fatigue and a wide range of other symptoms, so it may be that there are a variety of different POTS phenotypes, one (or more) or which manifest as the symptom of fatigue. An alternative explanation for the demographic differences between the two groups is related to referral bias.

Studies in adolescents suggest that POTS physiology underlies orthostatic intolerance in the majority of those with CFS.[3] Studies suggest that POTS is accompanied with a range of autonomic nervous system abnormalities including vagal withdrawal and enhanced sympathetic modulation, associated with findings consistent with pooling in the lower limbs, similar pathophysiological mechanisms as those hypothesized in a proportion of those with the diagnosis of CFS/ME.[12–14]

Our clinical impression is that treatment to reduce the heart rate in POTS is associated with improvements in fatigue.[22] This needs to be formally evaluated in randomized controlled trials in patients with CFS with a POTS phenotype.

We would suggest that the diagnosis of POTS (a potentially treatable condition) may be being missed in those attending services with CFS. Studies suggest that on follow-up, 80% of those with POTS will improve, 60% are functionally normal and 90% were able to return to work.[23,24] It is therefore important that this diagnosis is considered in all patients presenting with fatigue and that appropriate investigations performed. We would suggest that at the very minimum this includes haemodynamic assessment in response to standing of patients attending CFS/ME clinical services.

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*Conflict of interest*: None declared.

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