

Malmö POTS symptom score: Assessing symptom burden in postural orthostatic tachycardia syndrome

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Abstract. Spahic JM, Hamrefors V, Johansson M, Ricci F, Melander O, Sutton R, et al. Malmö POTS symptom score: Assessing symptom burden in postural orthostatic tachycardia syndrome. *J Intern Med.* 2022;**00**:1–9.

Background. Postural orthostatic tachycardia syndrome (POTS) is a common cardiovascular autonomic disorder characterized by excessive heart rate (HR) increase on standing and symptoms of orthostatic intolerance, posing significant limitations on functional capacity. No objective tool exists to classify symptom burden in POTS.

Methods. We conducted a case–control study in 62 POTS patients and 50 healthy controls to compare symptom burden between groups using the newly developed, self-rating, 12-item, Malmö POTS Score (MAPS; 0–10 per item, total range 0–120) based on patients own perception of symptoms through visual analogue scale assessment. We have also explored correlations between symptom severity assessed by MAPS, basic clinical parameters and postural haemodynamic changes.

Results. POTS patients showed significantly higher total MAPS score (78 ± 20 vs. 14 ± 12 , $p < 0.001$), higher baseline systolic blood pressure (BP), diastolic BP and HR ($p < 0.001$) compared with healthy controls. The most prominent symptoms in POTS were palpitations, fatigue and concentration difficulties. Haemodynamic parameters on standing were significantly correlated with palpitations in POTS after adjustment for age and sex (lower systolic and diastolic BP, and higher HR) ($p < 0.001$ for all). Orthostatic HR was significantly associated with concentration difficulties and total MAPS score. The optimal cut-point value of MAPS to differentiate POTS and healthy controls was ≥ 42 (sensitivity, 97%; specificity, 98%).

Conclusions. Symptom severity, as assessed by MAPS score, is fivefold higher in POTS compared with healthy individuals. The new MAPS score can be useful as a semiquantitative system to assess symptom burden, monitor disease progression and evaluate pre-test likelihood of disease.

Keywords: autonomic dysfunction, postural orthostatic tachycardia, POTS, scoring system, symptoms

Introduction

Postural orthostatic tachycardia syndrome (POTS) is a common multifaceted condition, characterized by autonomic dysfunction and an exaggerated adrenergic response in the upright position [1]. Prior to COVID-19, POTS affected an estimated 1–3 million individuals in the United States [2], predominantly young females aged 15–45 at diagnosis [3–5]. Current diagnostic criteria for POTS, outlined by the European Society of Cardiology

(ESC) Guidelines on Syncope, include symptoms of orthostatic intolerance for at least 3–6 months together with orthostatic heart rate (HR) increase >30 bpm (HR increase > 40 bpm in patients <19 years) or HR exceeding 120 bpm in upright position in the absence of orthostatic hypotension (ESC recommendation: Class IIa, level C) [4, 6].

The precise aetiology of POTS remains unknown, although the haemodynamic changes are thought

to reflect convergence of multiple pathophysiological processes including peripheral autonomic neuropathy, hypovolemia, elevated sympathetic tone, deconditioning and auto-antibodies to cardiovascular receptors [7]. Previous studies have shown that certain immunological stressors such as viral infections, trauma, surgery and pregnancy predispose to the onset of POTS, which suggest an autoimmune component in the pathophysiological pathway [3, 5]. Long-term prognosis is poorly explored, though around 50% of patients may experience symptom reduction or recover spontaneously within 1–3 years [3]. Recently, POTS has been indicated as a possible form of post-acute-COVID-19 sequelae [8–10].

Symptoms often include both cardiac symptoms (rapid palpitations, light-headedness, presyncope, chest discomfort, and dyspnoea) and non-cardiac symptoms (reduced concentration, brain fog, headache, nausea, fatigue, blurred vision, and exercise intolerance) [11]. Cardiovascular symptoms experienced by POTS patients are thought to reflect haemodynamic changes of upright posture [3]. Although the primary symptoms of POTS occur when standing and improve when sitting or lying, patients often have other chronic symptoms and comorbidities that cannot be explained by orthostatic intolerance including chronic fatigue, gastrointestinal disorders, nausea, fibromyalgia and joint hypermobility [12], contributing to the complexity of symptoms in POTS [5, 13–15].

To date, no objective tool exists to classify symptom burden and assess disease progression in POTS. Integrating the best evidence available with our clinical expertise, we aimed to design a symptom scoring system and test it in the setting of an established cohort of POTS patients.

Further, we explored the correlation between haemodynamic postural changes and symptoms at upright posture.

Methods

Study design and population

Patients with POTS were recruited from the Syncope Study of Unselected Population in Malmö (SYSTEMA) cohort, including over 2200 patients with unexplained syncope and/or orthostatic intolerance syndromes examined in a tertiary care centre in Malmö, Sweden between 2008 and 2021 [16]. The study population included 62 symptomatic

patients with disease history ≥ 6 months [3] and confirmed POTS diagnosis by head-up tilt test (HUT) on their first evaluation according to current European Society of Cardiology syncope guidelines [17]. Patients with POTS were excluded in the setting of POTS following COVID-19, iron deficiency, sleep disorders, endocrine disorders, arrhythmias, volume depletion and psychiatric illness.

Fifty healthy controls were recruited among staff members or volunteers at the study site and underwent an active standing test at the Clinical Research Unit of the Department of Internal Medicine, Skåne University Hospital, Malmö, Sweden. Healthy controls reported no symptoms of orthostatic intolerance and no history of syncope and were age- and sex-matched with the POTS group as closely as possible.

Investigation protocol

All participants were asked to discontinue cardiovascular medications (beta-blockers, ivabradine and midodrine) 48 h prior to testing. Fasting was started during the evening before, with unrestricted water consumption.

POTS patients were investigated with head-up tilt test. The protocol included supine rest for 10 min preceding table elevation to 60–70° for 20 min, and optional nitroglycerine provocation according to the Italian protocol, exclusively for patients with unexplained syncope and negative unmedicated phase of head-up tilt [18]. Beat-to-beat blood pressure and ECG were recorded continuously using a non-invasive validated method (Nexfin monitor, BMEYE, Amsterdam or Finapres Nova, Finapres Medical Systems, Enschede, The Netherlands) [19]. POTS diagnosis was defined by symptoms of orthostatic intolerance lasting for ≥ 6 months associated with pathological head-up tilt test or active standing test showing HR increase > 30 bpm (HR increase > 40 bpm in patients < 19 years) or HR exceeding 120 bpm in upright position (prior to nitroglycerine administration), within 10 min and in the absence of orthostatic hypotension [3].

Healthy controls were examined with active standing. Before initiating the active standing test, each participant had to lie quietly in a supine position for 10 min, after which baseline supine blood pressure and HR were measured. The subject was then asked to perform active standing for 10 min. Blood pressure was measured at 1, 3, 5 and 10 min

using an automatic BP monitor (Omron M6, Kyoto, Japan). An average of two measurements was used for group comparisons.

Malmö POTS symptom score

We developed a novel, questionnaire-based, symptom scoring system, the Malmö POTS Symptom Score (MAPS), for self-assessment of symptom burden using a visual analogue scale graded from 0 (no symptoms) to 10 (very pronounced symptoms), based on patients' own perception of 12 commonly reported symptoms: five cardiac symptoms (palpitations, dizziness, presyncope, dyspnoea and chest pain) and seven non-cardiac symptoms (gastrointestinal symptoms, insomnia, concentration difficulties, headache, myalgia, nausea and fatigue) during the previous 7 days (Supporting Information: MAPS questionnaire in original Swedish language and English translation). The selection of questions included in MAPS was based on available literature on self-reported symptomatology in POTS, expert opinion, and authors' own clinical experience [2, 3, 11, 12, 20–22]. Three co-authors (JS, VH and AF) analysed data from a large international POTS survey based on 4835 individual online questionnaires [20] and selected the most prevalent symptoms reported by at least 75% of participants. The symptoms were grouped into 12 main categories. Gastrointestinal symptoms were merged into one category (pain in the stomach, diarrhoea or constipation) as majority of POTS patients report varying and alternating symptoms from gastrointestinal tract. The questionnaire was preliminary tested on 10 consecutive newly diagnosed POTS patients who confirmed an adequate coverage of their POTS-related symptoms. The score ranges from 0 to a maximum score of 120 points (see Graphical Abstract).

All study participants were asked to complete the MAPS questionnaire. The total score was calculated for evaluation and comparison between POTS patients and healthy controls. Frequency distribution graphs for each symptom reported in the MAPS questionnaire are available in the Supporting Information.

Statistical analysis

Group characteristics were reported as mean and standard deviation or median and interquartile range, as appropriate, for continuous variables, and as counts and percentages for categorical variables. Between-groups comparison was per-

formed using independent samples *t*-test and Mann–Whitney *U* test, as appropriate.

Construct validity

Linear regression analysis was performed with individual symptom scores ($n = 12$) and total score as dependent variables, and following variables as independent variables: age, sex, duration of symptoms and haemodynamic parameters obtained during standing test in univariable and multivariable-adjusted models. The multivariable-adjusted model was created by entering age and sex as covariates. Receiver operating characteristics (ROC) curves were constructed to test the ability of MAPS to predict POTS status. The optimal cut-point value of MAPS score to discriminate between POTS and healthy controls was calculated by Youden method. *p*-Value of <0.05 was considered statistically significant. Data were analysed using SPSS software version 27 (SPSS, Chicago, IL, USA) and easyROC: an interactive web-tool for ROC curve analysis using R language environment, and OptimalCutpoints R package available from the Comprehensive R Archive Network (CRAN).

Ethics approval

This study complies with the Declaration of Helsinki. The study was approved by the Regional Ethical Committee in Lund, Sweden (82/2008; and 2017/295), and all study participants provided informed written consent.

Results

Baseline characteristics are shown in Table 1. Patients with POTS were younger (age 28 ± 9 years vs. age 32 ± 10 years; $p = 0.016$) and had higher baseline systolic blood pressure, diastolic blood pressure and HR compared with controls ($p < 0.001$) (Table 1). Female participants were strongly overrepresented in both groups, POTS (88.7%) and controls (82%).

Correlation of MAPS with symptom severity in POTS

POTS patients reported a fivefold higher symptom burden compared with controls (mean total MAPS score, 78 ± 20 vs. 14 ± 12 , $p < 0.001$) (Figures 1 and 2). The three most severe symptoms reported by POTS patients were palpitations (7.7 ± 1.7), fatigue (7.6 ± 2.5) and concentration difficulties (7.2 ± 2.1) (Figure 2), although all 12 symptom categories were distinctly elevated in POTS patients with an average score of at least five per category

Table 1. Baseline characteristics of the study population

Baseline characteristics ^a	POTS (n = 62)	Controls (n = 50)	p-Value
Age (years)	28 (9)	32 (10)	0.016
Female sex, n (%)	55 (89)	41 (82)	0.067
SBP supine, mmHg	125 (12)	114 (10)	<0.001
DBP supine, mmHg	76 (8)	69 (8)	<0.001
HR supine, bpm	82 (15)	64 (11)	<0.001
SBP standing 3 min, mmHg	127 (14)	113 (10)	<0.001
DBP standing 3 min, mmHg	89 (11)	75 (8)	<0.001
HR standing 3 min, bpm	115 (19)	81 (14)	<0.001

Note: Values are reported as mean (standard deviation) for continuous variables and as count (percentage) for categorical variables. p-Values for differences between the groups are shown.

Abbreviations: DBP, diastolic blood pressure; HR, heart rate; POTS, postural orthostatic tachycardia; SBP, systolic blood pressure.

^aHR and BP values here presented and compared were collected from head-up tilt test for POTS patients and from active standing for controls.

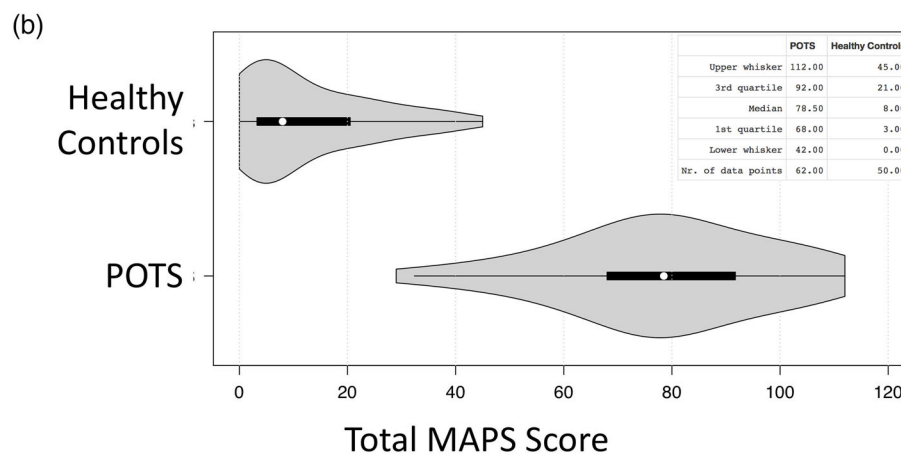
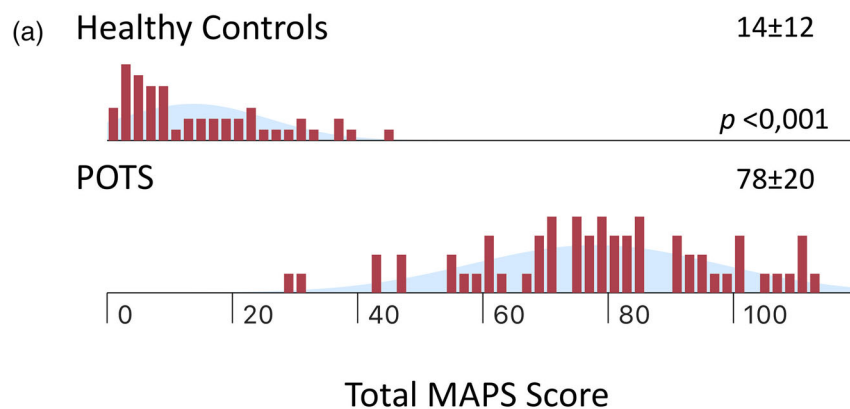


Fig. 1 Total Malmö POTS Symptom Score (MAPS) score in healthy controls and postural orthostatic tachycardia syndrome (POTS). The maximum score is 120, and the lowest 0. Distribution of MAPS score by (a) frequency bar chart and (b) violin plots.

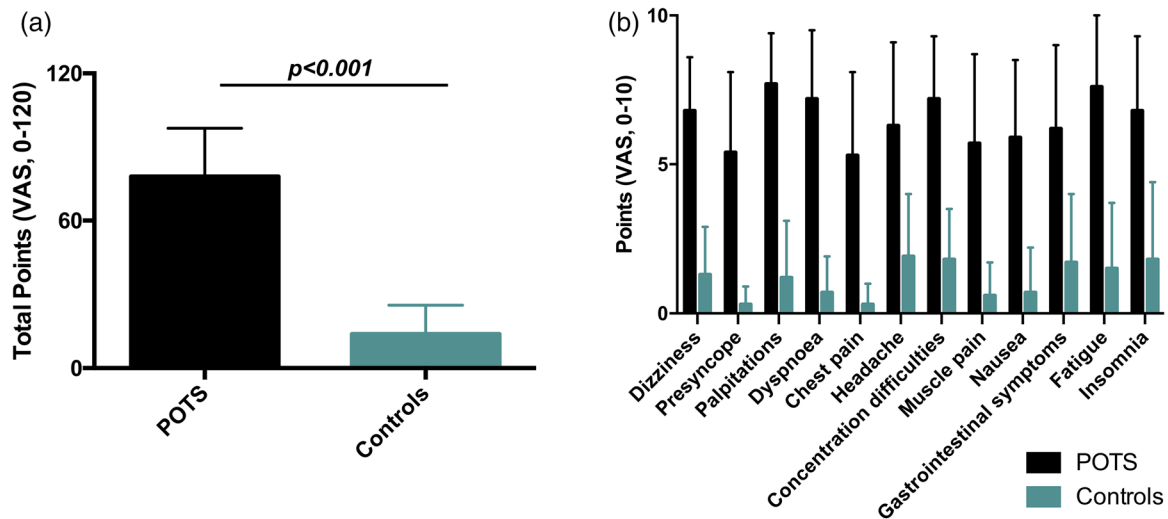


Fig. 2 Total Malmö POTS Symptom Score (MAPS) score and individual item scores. (a) Total MAPS score; (b) individual item scores: $p < 0.001$ for all pairwise comparisons. POTS, postural orthostatic tachycardia syndrome.

(see Graphical Abstract). In contrast, healthy controls reported the highest symptom burden due to headache (1.9 ± 2), concentration difficulties (1.8 ± 1.7) and insomnia (1.8 ± 2.6) (Figure 2). The optimal cut-off value to discriminate between POTS and healthy controls was a total MAPS score of ≥ 42 , yielding excellent sensitivity (97%; 95% confidence interval [CI] 0.89–0.99) and specificity (98%; 95% CI 0.89–0.99) (Figure 3).

Haemodynamic parameters and symptom severity by MAPS score

We observed a strong positive correlation between total MAPS score and orthostatic HR at 3 min of head-up tilt in POTS patients and during active standing for healthy controls (Figure 4). Likewise, we observed a significant increase of total MAPS score across supine and orthostatic HR quartiles in POTS compared with controls (Figure 5).

We found, furthermore, a significant correlation between all haemodynamic parameters (systolic blood pressure, diastolic blood pressure and HR) at 10 min of head-up tilt and symptoms in POTS compared with healthy controls in the univariate analysis ($p < 0.001$). After adjustment for age and sex, only palpitations remained significantly associated with all haemodynamic parameters in POTS ($p < 0.001$), whereas concentration difficulties were significantly associated with increased HR during head-up tilt in POTS patients ($p < 0.05$). Other

cardiovascular and non-cardiovascular symptom categories did not demonstrate significant associations with haemodynamic parameters, neither supine nor on standing.

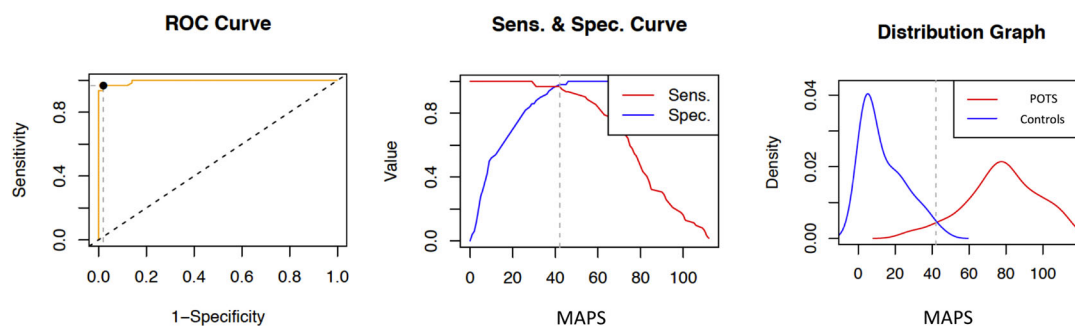
Discussion

In this study, we used the newly developed 12-item score Malmö Postural orthostatic tachycardia syndrome (POTS) score (MAPS) as a potential tool to assess the symptom severity in POTS patients by comparing the difference in symptom burden between POTS patients and healthy controls.

Notably, we observed a fivefold increase in symptom severity reported by patients with POTS compared with healthy controls in all symptom categories, which agrees with earlier studies confirming a decreased quality of life in POTS [5, 23, 24]. Currently, there are no clinical self-administered instruments specifically dedicated to evaluation of symptom burden in POTS. Those applied in the clinic and research are usually based on previous score systems created for other conditions such as autonomic failure or orthostatic hypotension and are inevitably associated with lesser precision.

In our study, patients with POTS were predominantly younger females, which is in line with previous studies [3–5, 25]. Also, all baseline haemodynamic parameters obtained during head-up tilt

MAPS Score Optimal Cut-Point: 42



MAPS score 42	Value	Lower Limit	Upper Limit
Sensitivity	0.968	0.888	0.996
Specificity	0.980	0.894	0.999
PPV	0.984	0.911	0.998
NPV	0.961	0.867	0.999
Positive LR	48.837	6.948	336.982
Negative LR	0.033	0.008	0.129

Fig. 3 Optimal cut-off point identification by Youden method to discriminate between healthy controls and postural orthostatic tachycardia syndrome (POTS). Total Malmö POTS Symptom Score (MAPS) ≥ 42 likely indicates pathology. LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

were significantly higher in POTS patients. Interestingly, we found that elevated HR and lower systolic and diastolic blood pressure at 10 min of head-up tilt were associated with more pronounced palpitations experienced by patients with POTS, whereas concentration difficulties were associated with elevated HR on standing. These findings in accordance with sympathetic overactivity in POTS patients and may be partly explained by increased circulating norepinephrine levels in these patients as shown by previous studies [26].

Considering the pathophysiology of POTS, we know that some subtypes of POTS are suggested to be related to hypovolemia and peripheral autonomic neuropathy [7]. The observed increase in HR can be seen both as a compensatory mechanism but also as a pathophysiological pathway where catecholamine release is a priori exaggerated [26]. Moreover, reported symptoms may reflect a reduction in the capacity to autoregulate cerebral blood flow and the metabolic sequelae of persistent tachycardia [27].

A previous study in 32 POTS patients used the Composite Autonomic Symptom Scale 31 (COMPASS-31) questionnaire [28], which is a validated tool assessing autonomic symptoms across six domains, initially established to assess symptoms of neurogenic autonomic disorders, found that the COMPASS-31 did not fully ascertain key symptoms relevant for assessment of POTS, and important differences occurred when applying COMPASS-31 to POTS with domain weighting deemphasizing certain significant symptoms relevant to POTS [29].

The generalized autonomic dysfunction together with fatigue and concentration difficulties [27] observed in POTS cannot be explained by single organ dysfunction but is likely a result of multiple mechanisms [15]. In this study, we have particularly noted the association between two main symptoms, palpitations, concentration difficulties and haemodynamic parameters on standing. HR increase seems to be the only parameter that is associated with both concentration

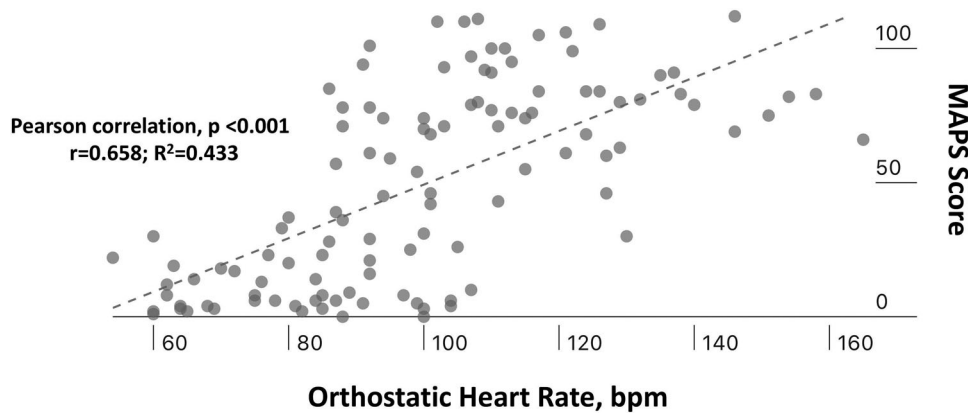


Fig. 4 Relationship between total Malmö POTS Symptom Score (MAPS) score and orthostatic heart rate. Heart rate was measured at 3 min of standing (head-up tilt test [HUT] for postural orthostatic tachycardia syndrome [POTS] and active standing for controls).

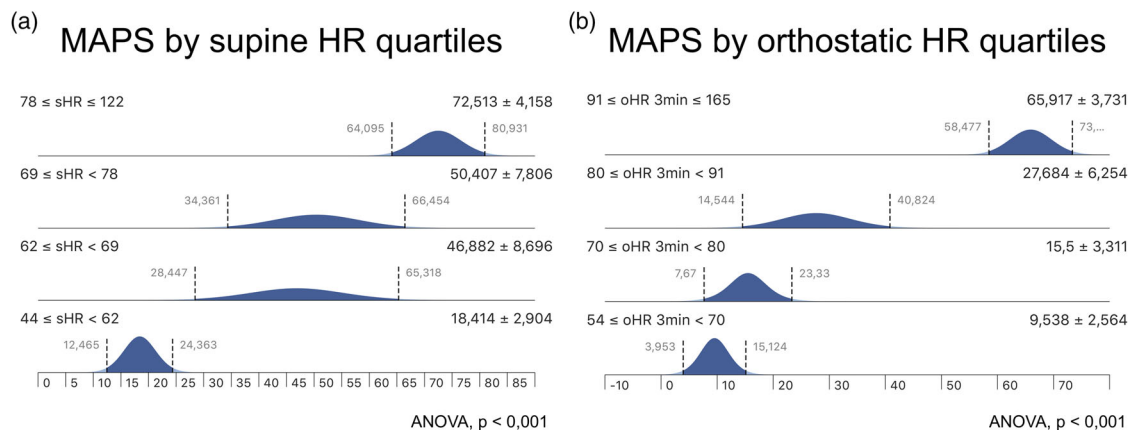


Fig. 5 Malmö POTS Symptom Score (MAPS) score by supine (panel a) and orthostatic (panel b) heart rate (HR) quartiles in the overall study population. HR was measured at 3 min of standing. HUT, head-up tilt test; oHR, orthostatic heart rate (bpm); POTS, postural orthostatic tachycardia syndrome; sHR, supine heart rate (bpm).

difficulties and palpitations, although blood pressure also seems to play an important part in symptom generation. We hypothesized that if vasoactive medications were added as a treatment strategy in patients showing signs of lower blood pressure during head-up tilt, compensatory tachycardia could possibly decrease and concentration difficulties improve. Thus, future studies assessing serial assessments using the MAPS symptom score in relation to treatment of POTS would be of interest.

Strengths and limitations

To date, no objective tool exists to gauge symptom burden, assess disease progression and

response to treatment in POTS. This is the first study to derive a questionnaire-based scoring system to assess severity of symptom in POTS. Further, MAPS score yields excellent specificity and sensitivity for classifying POTS. Moreover, the self-administered nature of the MAPS questionnaire eliminates possible interviewer bias associated with physician-assisted or health worker-assisted administration. This study is limited by its single-centre, observational nature and selection and referral biases. The score warrants external validation and replication in a larger multicentre setting. The group of POTS patients was highly selected, meaning that the results may not represent symptoms

presented by POTS patients with less pronounced disease.

Perspectives

POTS is a complex syndrome with symptoms of orthostatic intolerance significantly impacting and limiting the functional capacity. The newly developed MAPS score may be useful for the structured evaluation of symptom severity in patients with POTS. The observed increase in individuals reporting POTS-like symptoms following COVID-19 emphasizes the urgent need for an easily self-administered questionnaire, such as MAPS, to assess the severity of the syndrome [30]. Future prospective studies should aim to test the utility of MAPS score to evaluate pre-test likelihood of disease, to assess health-related quality of life, to track symptom progression/regression over time, to monitor the outcome of patients and to measure the effect of the therapies either for clinical purposes or for research. Additional studies are also necessary to validate the score in other populations and clinical settings. Finally, comparative studies using validated autonomic symptom scores such as COMPASS-31 and non-disease-specific questionnaires assessing the total functional capacity are warranted.

Conclusions

Patients with POTS report a broad-spectrum symptom burden significantly exceeding predefined normality when compared with healthy individuals, posing significant limitations on functional capacity. The newly developed Malmö POTS symptom score may be useful for the structured evaluation of symptom severity in patients with POTS, offering excellent specificity and sensitivity. Future studies are warranted to test the utility of MAPS score in other populations and clinical settings, and also to track symptom progression/regression and to monitor treatment response over time.

Acknowledgments

This work was supported by research grants from Region Skåne, Sweden, The Crafoord Foundation, The Swedish Heart and Lung Foundation, and governmental funding (ALF-funds, Sweden).

Funding

Region Skåne, Sweden; The Crafoord Foundation; The Swedish Heart and Lung Foundation; ALF-funds, Sweden.

Conflict of interest

Artur Fedorowski receives lecture fees from Medtronic Inc., Biotronik, and Finapres Medical Systems. Richard Sutton reports acting as a consultant to Medtronic Inc. and membership of the Speakers bureau of Abbott Laboratories (SJM) Corp. and holds stock in Boston Scientific Corp. and Edwards Lifesciences Corp. All other authors declare that there is no conflict of interest.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Supplement Material ■