Orthostatic Intolerance in Adults Reporting Long COVID Symptoms Was Not Associated With Postural Orthostatic Tachycardia Syndrome

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In this observational cross-sectional study, we investigated predictors of orthostatic intolerance (OI) in adults reporting long COVID symptoms. Participants underwent a 3-min active stand (AS) with Finapres® NOVA, followed by a 10-min unmedicated 70° head-up tilt test. Eighty-five participants were included (mean age 46 years, range 25–78; 74% women), of which 56 (66%) reported OI during AS (OI_AS). OI_AS seemed associated with female sex, more fatigue and depressive symptoms, and greater inability to perform activities of daily living (ADL), as well as a higher heart rate (HR) at the lowest systolic blood pressure (SBP) point before the first minute post-stand (mean HR_nadir: 88 vs. 75 bpm, \( P = 0.004 \)). In a regression model also including age, sex, fatigue, depression, ADL inability, and peak HR after the nadir SBP, HR_nadir was the only OI_AS predictor (OR = 1.09, 95% CI: 1.01–1.18, \( P = 0.027 \)). Twenty-two (26%) participants had initial (iOH) and 5 (6%) classical (cOH_AS) orthostatic hypotension, but neither correlated with OI_AS. Seventy-one participants proceeded to tilt, of which 28 (39%) had OI during tilt (OI_tilt). Of the 53 who had a 10-min tilt, 7 (13%) had an HR increase >30 bpm without cOH_tilt (2 to HR > 120 bpm), but six did not report OI_tilt. In conclusion, OI_AS was associated with a higher initial HR on AS, which after 1 min equalised with the non-OI_AS group. Despite these initial orthostatic HR differences, POTS was infrequent (2%). ClinicalTrials.gov Identifier: NCT05027724 (retrospectively registered on August 30, 2021).

Keywords: long COVID, orthostatic intolerance, haemodynamics, tilt table test, postural orthostatic tachycardia syndrome

INTRODUCTION

Long COVID or post-COVID-19 syndrome first gained recognition among social support groups and later in scientific and medical communities (Yong, 2021). This condition is not well understood as it affects COVID-19 survivors at all ages and levels of disease severity, with or without pre-existing comorbidities, and regardless of hospitalisation status (Vanichkachorn et al., 2021; Yong, 2021). A common symptom is fatigue, with or without organ-specific symptoms (Jennings et al., 2021; Rogers et al., 2021), which may result in negative impacts on resumption of functional and...
occupational activities (Yan et al., 2021). A systematic review reported that symptoms of mild COVID-19 may persist after 3 weeks in a third of patients (van Kessel et al., 2021). Another study reported that up to one in four patients with mild COVID-19 were still experiencing symptoms after 1 year (Rank et al., 2021); however, data on the exact prevalence and long-term effects of long COVID are still lacking (Zarei et al., 2021), with an urgent need for research in different populations and settings (Michelen et al., 2021). To aid clinicians and researchers, on October 6, 2021, the World Health Organization (WHO) issued a clinical case definition of post-COVID-19 condition, obtained by a Delphi consensus (WHO, 2021), as follows: “Post-COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others, which generally have an impact on everyday functioning. Symptoms may be new onset, following initial recovery from an acute COVID-19 episode, or persist from the initial illness. Symptoms may also fluctuate or relapse over time.”

The neurological and cardiovascular overlap in some long COVID symptoms, and in particular the reported occurrence of orthostatic intolerance (OI) (Dani et al., 2021; Paterson et al., 2021; Shah et al., 2021), have raised the hypothesis as to whether some long COVID patients could have measurable autonomic nervous system impairments (Del Rio et al., 2020; Goldstein, 2020; Keyhanian et al., 2020; Barizien et al., 2021; Becker, 2021; Larsen et al., 2021) such as orthostatic hypotension (OH) or postural orthostatic tachycardia syndrome (POTS) (Blitshteyn and Whitelaw, 2021; Johansson et al., 2021; Raj et al., 2021). In this light, we conducted a cross-sectional observational study on a cohort of participants reporting long COVID symptoms to fulfil the following objectives: (1) establish the prevalence of OI, both during an active stand (AS) test and a tilt test; (2) establish the prevalence of OH and POTS in this cohort; and (3) study haemodynamic and non-haemodynamic predictors of OI.

MATERIALS AND METHODS

Study and Cohort Description

This was a cross-sectional observational study on a participant cohort recruited for the TROPIC (Technology-assisted solutions for the Recognition of Objective Physiological Indicators of post-Coronavirus-19 fatigue) investigation at Trinity College Dublin and St James’s Hospital Dublin, Ireland. The study received full ethical and regulatory approvals. For the reporting, we followed STROBE guidelines (von Elm et al., 2007).

Participants were eligible for inclusion under all the following criteria: (1) age 18 years or older; (2) self-reported history of SARS-CoV-2 infection; (3) experiencing prolonged symptoms such as fatigue; (4) able to mobilise independently (with or without aid); (5) able to transfer independently or with minimal assistance of one person from lying to standing; and (6) able to give informed consent.

Participants were recruited from the following sources in our hospital: (1) falls and syncope unit; (2) geriatric day hospital; (3) post-COVID-19 outpatient clinic; (4) staff who had contracted COVID-19; and (5) participants from earlier post-COVID-19 research who had consented to be contacted for further studies. In addition, we also considered (6) self-referrals. COVID-19 and non-COVID-19 exclusion criteria for enrolment are outlined in the section 1 in Supplementary Material.

Prior to enrolment, participants were provided with a Participant Information Leaflet explaining the aims and procedures of the study. All participants provided explicit, informed, and voluntary consent to partake in the study, were explained the benefits and risks of participating in the research, and had the opportunity to discuss the study and ask questions. Participants were given the opportunity to withdraw from the study at any point and to forego completing components of the assessment protocol as desired.

Procedures

Participants underwent a 3-min AS with Finapres® NOVA, followed by a 10-min unmedicated 70° head-up tilt test. During both, participants had frontal lobe oxygenation monitoring via PortaLite® near-infrared spectroscopy (NIRS). All testing procedures complied with the local hand hygiene, sanitation, personal protective equipment (PPE), and research training protocols. We also considered international best practice recommendations for autonomic testing during the COVID-19 pandemic (Figueroa et al., 2020; Guaraldi et al., 2020; Sinn et al., 2021).

For the active stand, participants underwent a lying-to-standing orthostatic test with non-invasive beat-to-beat blood pressure monitoring using digital photoplethysmography (Finapres® NOVA, Finapres Medical Systems, Amsterdam, Netherlands). The height correction unit was zeroed and implemented as per manufacturer’s specifications. A 5-lead continuous electrocardiogram (ECG) was acquired throughout the test. During the supine rest period, an oscillometric brachial blood pressure measurement was obtained from the non-monitored (right) arm for calibration purposes, once the PhysioCal repetition rate was 70 beats or more (Wesseling, 1996). After at least 5 min of uninterrupted supine rest, a total lying duration of no more than 10 min, and a 10-s countdown, participants were asked to stand, unaided, as quick as possible. The PhysioCal was turned off just before the stand and switched back on at 1-min post-stand. After standing, systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were monitored for 3 min. Throughout the recording, participants were asked to remain motionless and in silence, except for reporting any symptoms of concern, with the monitored arm (left) resting extended by the side. Immediately after the stand, and at the end of the test, participants were asked to report whether they had felt any symptoms of dizziness, light-headedness, palpitations, or any other abnormal symptoms.

For the tilt procedure, which was medically supervised and started after a brief non-monitored break following AS, participants were affixed to an electrically motorised tilt table with footboard support and approximately 10 s of travel time between
orthostatic manoeuvre and prior to the first-minute post-stand; in the case of AS, they were noted at the lowest point of SBP following completion of the head-up tilt manoeuvre and prior to the first-minute post-tilt. For the AS, we also modelled the peak HR after the nadir SBP, defined as the maximum of the HR readings obtained at 1, 2, and 3 min. NIRS values were noted following the same SOP from a laptop display connected to the PortaLite® device via OxySoft® software (version 3.2.70), from which we extracted Tissue Saturation Index (TSI) values as the percentage ratio of oxygenated haemoglobin concentration to the total concentration of haemoglobin (Claffey et al., 2020).

Orthostatic Intolerance
For both AS and tilt, OI was defined as self-reported symptoms of dizziness, light-headedness, palpitations, or any other new abnormal symptoms occurring after the orthostatic manoeuvre.

Orthostatic Hypotension Definitions
Initial orthostatic hypotension (iOH) on AS was defined as a difference of >40 mmHg SBP and/or >20 mmHg DBP between baseline and nadir values (Freeman et al., 2011).

Classical orthostatic hypotension on AS (cOHAS) was defined as a difference of ≥20 mmHg SBP and/or ≥10 DBP between each baseline value and its minimum reading between minutes 1, 2, and 3 (Freeman et al., 2011; Brignole et al., 2018). Nadir values were not included in this definition for clear differentiation with iOH and to better reflect cOHAS as normally measured in routine clinical practice with an interval measurement device (Breeuwsma et al., 2018).

Classical orthostatic hypotension on tilt (cOHtilt) was defined as a difference of ≥20 mmHg SBP and/or ≥10 DBP between each baseline value and its minimum reading between nadir and minutes 1, 2, and 3. Nadir was included in this case because iOH is only associated with active rising (Wieling et al., 2007).

Postural Orthostatic Tachycardia Syndrome Definition
We computed the maximum HR between nadir and minutes 1–10 (or the available minutes in case of early tilt termination), to which we subtracted baseline HR. POTS was defined as HR increase >30 bpm or to >120 bpm within 10 min of tilt in the absence of OHAS and presence of OItilt (Freeman et al., 2011; Brignole et al., 2018).

Other Measures
For the characterisation of the cohort, we collected measures including:

- Demographics: age, sex.
- Anthropometrics: body mass index (BMI) (kg/m²).
- Proportion of third level education (i.e., primary university degree or higher).
- Past medical history including previous or current smoker, hypertension, heart disease (e.g., previous heart attack, angina, congestive heart failure, atrial fibrillation), diabetes mellitus (yes or no).
- Current medications including being on an antihypertensive, beta blocker, antidepressant, or benzodiazepine (yes or no).
- COVID-19 history: date of COVID-19 diagnosis; hospitalisation status (at least 1 overnight stay: yes or no); current symptomatology (from a structured questionnaire including 41 possible symptoms: yes or no for each), and interference with activities of daily living (ADL) (“In the past month, I have had too little energy to do the things I wanted to do”: yes or no).
- The 11-item Chalder Fatigue Scale (CFQ), a self-rating scale developed to measure the severity of physical and mental fatigue (Cella and Chalder, 2010). We employed the Likert scoring system, with an overall scale range from 0 (minimum) to 33 (maximum fatigue).
- The 20-item Center for Epidemiological Studies Depression (CES-D) scale (Radloff, 1977). Scores range from 0 to 60, with higher scores indicating greater depressive symptoms.
- The 22-item Impact of Event Scale—Revised (IES-R) (Creamer et al., 2003), which measured post-traumatic stress disorder (PTSD) symptoms in specific relation to participants’ COVID-19 illness (minimum: 0; maximum: 88).
- Five chair stands time as a measure of functional lower extremity strength (Munoz-Bermejo et al., 2021): time (in seconds) it took a participant to transfer as quick as possible
from a seated to a standing position and back to sitting five times.

**Statistical Analyses**

Statistics were computed with IBM® SPSS® Statistics for Windows, Version 26.0, Armonk, NY: IBM Corp. Descriptives were given with count and percentage (%), mean with standard deviation (SD), median with interquartile range (IQR), and range. Normality of continuous variables was assessed with the one-samples Kolmogorov–Smirnov test. We utilised the SPSS Chart Builder to visualise haemodynamic differences between subgroups via cluster line chart with representation of 95% confidence intervals (CI) around means. To compare characteristics between subgroups, we utilised the non-parametric two-sided Mann–Whitney U test for non-normally distributed continuous variables, and the Chi-square test for dichotomous characteristics. In the latter case, we used the 2-sided Fisher’s exact test when at least one cell had an expected count of <5. In addition, considering the repeated measures nature of the haemodynamic data, we conducted two-way ANOVA tests and calculated the within-subjects’ effects P-values (sphericity-assumed) for the interaction between time and OI groups. Bonferroni was the post hoc test used for pairwise comparisons. To establish independent predictors of dichotomous group membership, we computed logistic regression models, and for each predictor extracted the Odds Ratio (OR) and 95% CI for the OR. Multicollinearity checks were conducted. Statistical significance was defined as $P < 0.05$.

**Ethical Approval**

This study received full approval by the St James’s Hospital/Tallaght University Hospital Joint Research Ethics Committee (Submission Number: 104: TROPIC; Approval Date: May 4, 2021) and the St James’s Hospital Research & Innovation Office (Reference: 6566; Approval Date: May 14, 2021). The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All participants gave their informed consent prior to their inclusion in the study. All aspects of the study were executed in compliance with the General Data Protection Regulation (GDPR), and Irish regulations including the Health Research Regulations and the Data Protection Act 2018.

**RESULTS**

Of 92 consecutive participants recruited to the study between May and September 2021, 85 (92.4%) had the AS. Mean age was 46.0 years (SD 10.2, range 25–78), and 63 (74.1%) were women. Overall, fatigue was a very prevalent long COVID symptom (96.3%) reporting too little energy to do the things they wanted to do in the past month.

In terms of the haemodynamic comparison between OI and non-OI subgroups (Table 2), participants reporting OI had a higher HR at the lowest SBP point before the first-minute post-stand (mean HR$_{nadir}$ = 88 vs. 75 bpm, $P = 0.004$; two-way ANOVA: $P < 0.001$ for the main effect of time, $P = 0.006$ for the interaction OI$_{nadir}$×time, and $P = 0.033$ for the Bonferroni-adjusted post hoc analysis). There were no baseline or subsequent HR differences, or any BP or NIRS differences. In the haemodynamic visualisation in Figure 1, participants’ finishing BP levels (at 3 min) seemed higher than at baseline, with 95% CIs around means that clearly did not overlap in the case of DBP (panel B), but without any suggested differences between OI and non-OI subgroups. On closer inspection, for the overall cohort, there was a statistically significant difference between baseline and 3-min DBP (mean 81.0 vs. 93.1 mmHg, paired-samples t-test $P < 0.001$).

In the logistic regression model to investigate predictors of OI (Table 3), the only significant predictor after controlling for age, sex, fatigue, depression, ADL inability, and peak HR after the nadir SBP, HR$_{nadir}$, was the only OI predictor (OR = 1.09, 95% CI: 1.01–1.18, $P = 0.027$).

Of the 85 participants who had the AS, 71 (83.5%) had a tilt table test. In a survey, 14 participants did not have a tilt for reasons including history of recurrent vasovagal syncope (at
least two lifetime episodes), a body weight >120 kg (tilt table safety limit) or not consenting. All tilt participants had had the AS test. Of them, 28 (39.4%) had OI during tilt (OIAS). The frequencies of OIAS symptoms were as follows: “slightly light-headed” (n = 10, 35.7%), “light-headed” (n = 8, 28.6%), “slightly dizzy” (n = 3, 10.7%), “dizzy” (n = 2, 7.1%), “very light-headed” (n = 1, 3.6%), “palpitations” (n = 1, 3.6%), “head spinning” (n = 1, 3.6%), “drained” (n = 1, 3.6%), and “weak” 1 (n = 1, 3.6%). No instances of arrhythmia or acute myocardial ischaemia were detected in the continuous ECG trace. As regards OI agreement between AS and tilt, 78.6% (n = 22) of those who had OIAS had previously reported OIAS (P = 0.902). Of the 53 who had a 10-min tilt, 13% had an HR increase > 30 bpm without OH AS (2 to HR > 120 bpm), but six did not report OIAS. POTS was therefore present in n = 1 (1.9%). In the 18 participants whose tilt was terminated early, none of the available data fulfilled POTS criteria. As shown in the Supplementary Material, there were no statistically significant differences between OIAS subgroups across other clinical (section 2) or haemodynamic characteristics (sections 3, 4), and no significant predictors of OIAS in the regression model (section 5).

### DISCUSSION

In this study, we investigated predictors of OI in adults reporting long COVID symptoms. OI during active stand (OIAS) was reported by 66% of our sample and seemed associated with female sex, more fatigue and depressive symptoms, and greater inability to perform ADL, as well as a higher heart rate at the lowest systolic blood pressure point before the first-minute post-stand (HR nadir). In a regression model also including age, sex, fatigue, depression, ADL inability, and peak HR after the nadir SBP, HR nadir was the only OIAS predictor. 26% of participants had initial and 6% cOH AS, but neither correlated with OIAS. Of the
participants who had a tilt, 39% had OI during tilt, and 33% had cOHnadir and of the participants who completed a 10-min tilt, only 2% (n = 1) fulfilled POTs criteria.

The HR at the time of nadir SBP after stand seemed more important than the peak HR after the nadir SBP as a predictor of OI

| TABLE 2 | Haemodynamic comparison between OI and non-OI subgroups. |
| --- | --- | --- |
| **No OI** (initia | **OI** | **P** |
| n = 29 | (initial and final | | |
| Mean oscillometric baseline SBP, mmHg (SD) | 131.9 (13.3) | 131.2 (15.0) | 0.541<sup>a</sup> |
| Mean oscillometric baseline HR, bpm (SD) | 75.8 (13.3) | 77.8 (20.2) | 0.868<sup>b</sup> |
| Mean oscillometric baseline DBP, mmHg (SD) | 80.7 (7.9) | 80.9 (9.7) | 0.700<sup>a</sup> |
| Mean oscillometric baseline TSI, % (SD) | 67.4 (11.0) | 71.4 (12.9) | 0.210<sup>a</sup> |
| Mean oscillometric baseline HR, bpm (SD) | 74.6 (12.3) | 84.8 (19.6) | 0.004<sup>c</sup> |
| Mean oscillometric baseline DBP, mmHg (SD) | 80.9 (9.7) | 80.9 (9.7) | 0.700<sup>a</sup> |
| Mean oscillometric baseline TSI, % (SD) | 67.4 (11.0) | 71.4 (12.9) | 0.210<sup>a</sup> |
| Mean oscillometric baseline HR, bpm (SD) | 74.6 (12.3) | 84.8 (19.6) | 0.004<sup>c</sup> |
| Mean oscillometric baseline DBP, mmHg (SD) | 80.9 (9.7) | 80.9 (9.7) | 0.700<sup>a</sup> |
| Mean oscillometric baseline TSI, % (SD) | 67.4 (11.0) | 71.4 (12.9) | 0.210<sup>a</sup> |
| Mean oscillometric baseline HR, bpm (SD) | 74.6 (12.3) | 84.8 (19.6) | 0.004<sup>c</sup> |

<sup>a</sup>Active stand; OI, orthostatic intolerance during AS; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; bpm, beats per minute; TSI, tissue saturation index. Two of the 85 participants had a rise in DBP ≥ 10 mmHg within 3 min following AS (Jordan et al., 2020). The pathological significance of this finding is not clear and merits further investigation; indeed, orthostatic hypertension has been found in healthy subjects but also associated with higher (including hypertension) (Jordan et al., 2020) and lower (Wijkman et al., 2016) cardiovascular risks, with more research still needed to clarify its mechanisms and impacts (Jordan et al., 2020). Interestingly, even though orthostatic hypertension did not seem related to OI in our cohort, it has been described that some patients with chronic OI develop symptoms despite a hypertensive response to standing, suggesting that the chronic OI may somehow be elicited by central responses to the inappropriate tachycardia, even in the absence of any actual reduction in perfusion pressure (Narkiewicz and Somers, 1998).
In a previous study where autonomic testing was conducted a median of 119 days following acute COVID-19 infection, 22% of patients fulfilled the criteria for POTS (Shouman et al., 2021), in contrast with 2% in our sample with a median delay to testing of 302 days. While six of our seven tilt participants with HR increase >30 bpm and without OH$_{tilt}$ had chronic symptoms of OI lasting at least 6 months, only one had OI$_{tilt}$ during testing. A previous case report showed no improvement in COVID-19-associated POTS symptoms approximately 5.5 months after symptom onset (Miglis et al., 2020); in a case series of 20 patients, it was reported that most (85%) self-reported residual symptoms 6–8 months after COVID-19, although many felt that they had improved (Blitshteyn and Whitelaw, 2021). Three case reports have documented improvement in POTS after COVID-19 infection, with or without pharmacological support (Ishibashi et al., 2021; Ocher et al., 2021; O’Sullivan et al., 2021). To build on the anecdotal evidence, longitudinal studies are required to assess the evolution of post-COVID POTS in the same cohorts.

**FIGURE 1** | Continued
Our study has several important limitations. Firstly, from a study design perspective, generalisability of the findings cannot be assumed given the non-probabilistic recruitment. The evidence we presented is cross-sectional and observational, hence causation cannot be inferred. In addition, we did not have a sample of controls, which can be beneficial in the study of long COVID (Amin-Chowdhury and Ladhani, 2021). Statistical underpower is likely, given the many instances where the statistic of choice for comparisons was the Fisher's exact test, and a small sample size that precluded inclusion of a greater number of predictors in the regression models. Whilst we did not conduct an \textit{a priori} calculation of the sample size, we performed a \textit{post hoc} power calculation analysis for the main positive finding of the study, namely the difference in nadir HR between the two OIAS.

**FIGURE 1** | Haemodynamic visualisation of OI\textsubscript{AS} (n = 56) and non-OI\textsubscript{AS} (n = 29) groups. (A) Systolic blood pressure (SBP). (B) Diastolic blood pressure (DBP). (C) Heart rate (HR). (D) Tissue saturation index (TSI). bpm, beats per minute; CI, confidence interval.
From a haemodynamic data processing is often the case for tilts used in clinical practice to look for full symptom reproduction. From a haemodynamic data processing point of view, other studies have extracted the raw data from the Finapres® and performed signal averaging prior to analyses, for example in 5-s bins (van der Velde et al., 2007). While post hoc signal averaging can theoretically reduce the risk of spurious observations due to signal artefacts (Finucane et al., 2019), in this study we followed the direct observation method that is routinely utilised in clinical practice for the contemporaneous clinical assessment of patients.

In conclusion, in this cohort of participants reporting long COVID symptoms, the prevalences of OI during AS and tilt test were 66 and 39%, respectively. The prevalences of initial and classic OH during AS were 26 and 6%, respectively. Classic OH during tilt was present in 33%, and POTS was only present in 2%. OI\textsubscript{AS} was associated with a higher initial HR on AS, which after 1 min equalised with the non-OI\textsubscript{AS} group. The burden of psychological symptoms in this cohort was high and findings may be related to interoceptive mechanisms. However, our findings require external replication. More research is required to understand the mechanisms and long-term prognosis of autonomic function in long COVID, to better delineate therapies and estimate the need for services.

**DATA AVAILABILITY STATEMENT**

The datasets presented in this article are not readily available because of the conditions of the ethical approval. Requests to access the datasets should be directed to RRO, romeroor@tcd.ie.

**ETHICS STATEMENT**

This study involving human participants was reviewed and approved by St James's Hospital/Tallaght University Hospital Joint Research Ethics Committee (Submission Number: 104: TROPIC; Approval Date: 4 May 2021) and the St James's Hospital Research and Innovation Office (Reference: 6566; Approval Date: 14 May 2021). The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All participants gave their informed consent prior to their inclusion in the study. All aspects of the study were executed in compliance with the General Data Protection Regulation (GDPR), and Irish regulations including the Health Research Regulations and the Data Protection Act 2018. The participants provided their written informed consent to participate in this study.

**AUTHOR CONTRIBUTIONS**

RR-O and AM: conceptualisation. RR-O, AM, and LB: methodology. AM, GJ, FX, ED, and RR-O: clinical data collection. RR-O, AM, GJ, and ED: formal analysis and investigation. RR-O: writing—original draft preparation and funding acquisition. AM, GJ, FX, ED, and LB: writing—review and editing. RR-O and LB: resources. ED, LB, and RR-O: supervision. All authors contributed to the article and approved the submitted version.

**TABLE 3** | Logistic regression model with predictors of OI\textsubscript{AS}.

| OR   | 95% CI for OR | \( P \) |
|------|---------------|--------|
|     | Lower | Upper |
| Age | 0.98  | 0.91  | 1.05  | 0.604 |
| Female sex | 1.97  | 0.32  | 12.06 | 0.463 |
| CFQ score | 0.96  | 0.80  | 1.16  | 0.666 |
| CES-D score | 1.07  | 0.99  | 1.16  | 0.080 |
| In the past month, I have had too little energy to do the things I wanted to do | 4.48  | 0.32  | 62.08 | 0.263 |
| HR at nadir | 1.09  | 1.01  | 1.18  | 0.027 |
| Peak HR after the nadir SBP | 0.97  | 0.89  | 1.06  | 0.495 |

\( \text{AS, active stand}; \text{CFQ, Chalder Fatigue Scale}; \text{CES-D, Center for Epidemiological Studies Depression scale}; \text{HR, heart rate}; \text{SBP, systolic blood pressure}; \text{OR, odds ratio}; \text{CI, confidence interval.} \)
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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2022.833650/full#supplementary-material
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Supplementary Material

1 COVID-19 and non-COVID-19 exclusion criteria for enrolment.

COVID-19-related exclusion criteria were: (1) being in the acute COVID-19 phase and/or experiencing any of the following symptoms/situations included in a COVID-19 Health Screening Assessment Tool administered prior to enrolment: (2) new cough or shortness of breath, fever or chills within the last 48 hours; (3) new loss/distortion/alteration of sense of smell or taste; sore throat/swollen glands; new headaches; vomiting; diarrhoea; (4) positive COVID-19 test in the last 14 days; (5) awaiting a test result for COVID-19; (6) in close contact with someone who had COVID-19 symptoms in the last 14 days; (7) visit to a residential institution in the last 14 days where ongoing COVID-19 transmission had been confirmed; (8) being from a geographical region where there was ongoing COVID-19 transmission and on lockdown/travel restriction; (9) international travel in the last 14 days; or (10) any other symptoms/situations as per Principal Investigator’s clinical judgement.

Non-COVID-19 exclusion criteria were: (11) being pregnant; (12) cognitive impairment/dementia with inability to give informed consent; (13) upper limb lymphoedema (cuff-site); and (14) severe skin allergies to adhesive tapes. The following were contra-indications for tilt testing: (15) stroke or acute myocardial infarction within the past 90 days (or any other acute cardiac event); (16) unstable angina; (17) uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise; (18) uncontrolled symptomatic heart failure; (19) symptomatic severe aortic stenosis; (20) suspected or known dissecting aortic aneurysm; (21) acute myocarditis or pericarditis; (22) acute pulmonary embolus or pulmonary infarction; (23) patients in whom low organ perfusion pressures may compromise end-artery supplied tissue; (24) severe left ventricular outflow obstruction; and (25) critical mitral stenosis. In addition, for safety reasons, participants who during the anamnesis reported a history of (26) recurrent vasovagal syncope (at least two lifetime episodes) or had a (27) body weight >120 Kg were excluded from tilt testing.
Comparison between OI_{tilt} and non-OI_{tilt} subgroups. OI_{tilt}: orthostatic intolerance during tilt; OI_{AS}: orthostatic intolerance during active stand; SD: standard deviation; BMI: body mass index; IQR: interquartile range; CFQ: Chalder Fatigue Scale; CES-D: Center for Epidemiological Studies Depression scale; IES-R: Impact of Event Scale – Revised; cOH_{tilt}: classical orthostatic hypotension during tilt; POTS: postural orthostatic tachycardia syndrome.

| Characteristic                          | No OI_{tilt} (n=43) | OI_{tilt} (n=28) | P     |
|-----------------------------------------|---------------------|------------------|-------|
| Mean age, years (SD)                    | 47.1 (10.6)         | 44.1 (9.7)       | 0.281 |
| Female sex (%)                          | 69.8                | 75.0             | 0.632 |
| Third level education (%)               | 65.9                | 63.0             | 0.807 |
| Previous or current smoker (%)          | 51.3                | 40.7             | 0.399 |
| History of hypertension (%)             | 20.9                | 14.3             | 0.470 |
| History of heart disease (%)            | 4.7                 | 0.0              | 0.515 |
| History of diabetes (%)                 | 7.0                 | 0.0              | 0.273 |
| Median days post-COVID-19 diagnosis (IQR) | 269.0 (327.0)      | 234.0 (339.5)    | 0.767 |
| Hospitalised with COVID-19 (%)          | 26.8                | 26.9             | 0.993 |
| Median CFQ score (IQR)                  | 25.5 (9.8)          | 25.0 (8.5)       | 0.994 |
| Median CES-D score (IQR)                | 19.0 (16.5)         | 23.0 (19.0)      | 0.267 |
| Median IES-R score (IQR)                | 22.0 (31.0)         | 26.0 (31.0)      | 0.585 |
| Mean BMI, kg/m^2 (SD)                   | 28.0 (5.4)          | 28.6 (4.9)       | 0.410 |
| Mean 5-chair stands time, seconds (SD)  | 14.8 (10.5)         | 13.8 (9.3)       | 0.827 |
| OI_{AS}                                 | 51.2                | 78.6             | 0.020 |
| cOH_{tilt}                              | 31.0                | 32.1             | 0.916 |
| HR increase >30 bpm without OH_{AS}     | 14.3                | 3.7              | 0.233 |
| On antihypertensive (%)                 | 18.6                | 14.3             | 0.753 |
| On beta blocker (%)                     | 9.3                 | 21.4             | 0.177 |
| On antidepressant (%)                   | 11.6                | 28.6             | 0.071 |
| On benzodiazepine (%)                   | 2.3                 | 3.6              | 0.100 |

*a 2-sided Mann-Whitney U test; b Chi-square test; c 2-sided Fisher’s exact test; * statistically significant (P<0.05)
3  Haemodynamic comparison between OI tilt and non-OI tilt subgroups. OI tilt: orthostatic intolerance during tilt; SD: standard deviation; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; bpm: beats per minute; TSI: tissue saturation index.

|                                | No OI (initial n=43)                        | OI (final n=15)                           | P     |
|--------------------------------|--------------------------------------------|-------------------------------------------|-------|
| Mean oscillometric baseline SBP, mmHg (SD) | 81.2 (9.4) (range 66 – 104)                | 83.9 (9.8) (range 64 – 99)                | 0.169 |
|                                 | Tilt: mean baseline SBP, mmHg (SD)         | 78.3 (10.5)                               | 0.494 |
|                                 | Tilt: mean nadir SBP, mmHg (SD)           | 81.6 (14.2)                               | 0.685 |
|                                 | Tilt: mean DBP at 1 minute, mmHg (SD)     | 84.6 (11.0)                               | 0.818 |
|                                 | Tilt: mean DBP at 2 minutes, mmHg (SD)    | 88.1 (14.4)                               | 0.494 |
|                                 | Tilt: mean DBP at 3 minutes, mmHg (SD)    | 87.0 (12.4)                               | 0.347 |
|                                 | Tilt: mean DBP at 4 minutes, mmHg (SD)    | 89.0 (14.9)                               | 0.479 |
|                                 | Tilt: mean DBP at 5 minutes, mmHg (SD)    | 86.6 (13.9)                               | 0.016 |
|                                 | Tilt: mean DBP at 6 minutes, mmHg (SD)    | 88.1 (14.4)                               | 0.705 |
|                                 | Tilt: mean DBP at 7 minutes, mmHg (SD)    | 88.5 (15.4)                               | 0.536 |
|                                 | Tilt: mean DBP at 8 minutes, mmHg (SD)    | 89.0 (12.3)                               | 0.913 |
|                                 | Tilt: mean DBP at 9 minutes, mmHg (SD)    | 88.9 (13.1)                               | 0.655 |
|                                 | Tilt: Mean baseline HR, bpm (SD)           | 67.4 (10.0)                               | 0.337 |
|                                 | Tilt: mean nadir HR, bpm (SD)             | 74.7 (15.2)                               | 0.193 |
|                                 | Tilt: mean HR at 1 minute, bpm (SD)       | 77.6 (14.5)                               | 0.341 |
|                                 | Tilt: mean HR at 2 minutes, bpm (SD)      | 78.2 (14.3)                               | 0.812 |
|                                 | Tilt: mean HR at 3 minutes, bpm (SD)      | 78.5 (14.6)                               | 0.934 |
|                                 | Tilt: mean HR at 4 minutes, bpm (SD)      | 78.6 (13.4)                               | 0.933 |
|                                 | Tilt: mean HR at 5 minutes, bpm (SD)      | 80.7 (13.6)                               | 0.942 |
|                                 | Tilt: mean HR at 6 minutes, bpm (SD)      | 80.3 (13.3)                               | 0.738 |
|                                 | Tilt: mean HR at 7 minutes, bpm (SD)      | 80.6 (14.1)                               | 0.925 |
|                                 | Tilt: mean HR at 8 minutes, bpm (SD)      | 80.0 (14.2)                               | 0.548 |
|                                 | Tilt: mean HR at 9 minutes, bpm (SD)      | 81.7 (14.9)                               | 0.428 |
|                                 | Tilt: mean HR at 10 minutes, bpm (SD)     | 80.3 (14.8)                               | 0.724 |
|                                 | Tilt: mean baseline TSI, % (SD)           | 70.0 (4.7) (range 56 – 79)                | 0.450 |
|                                 | Tilt: mean nadir TSI, % (SD)              | 69.1 (5.1)                                | 0.793 |
|                                 | Tilt: mean TSI at 1 minute, % (SD)        | 68.9 (4.5)                                | 0.521 |
|                                 | Tilt: mean TSI at 2 minutes, % (SD)       | 67.9 (5.0)                                | 0.677 |
|                                 | Tilt: mean TSI at 3 minutes, % (SD)       | 67.9 (5.8)                                | 0.868 |
|                                 | Tilt: mean TSI at 4 minutes, % (SD)       | 68.1 (6.0)                                | 0.577 |
|                                 | Tilt: mean TSI at 5 minutes, % (SD)       | 68.0 (6.0)                                | 0.515 |
|                                 | Tilt: mean TSI at 6 minutes, % (SD)       | 68.4 (5.5)                                | 0.091 |
|                                 | Tilt: mean TSI at 7 minutes, % (SD)       | 68.5 (5.4)                                | 0.155 |
|                                 | Tilt: mean TSI at 8 minutes, % (SD)       | 69.0 (5.6)                                | 0.132 |
|                                 | Tilt: mean TSI at 9 minutes, % (SD)       | 68.7 (5.3)                                | 0.142 |
|                                 | Tilt: mean TSI at 10 minutes, % (SD)      | 63.9 (4.0)                                | 0.892 |

18 of the 71 participants had an early tilt termination (n=2 before the 2nd minute, n=3 before the 3rd minute, n=1 before the 4th minute, n=2 before the 5th minute, n=5 before the 6th minute, n=2 before the 8th minute, and n=3 before the 10th minute). Of the early terminations, 3 did not relate to symptom development (n=3). 1 2-sided Mann-Whitney U test; 2 Chi-square test; * statistically significant (P<0.05). Two-way ANOVA P values for the interaction:

SBP: P=0.095; DBP: P=0.280; HR: P=0.494; TSI: P=0.219.
Haemodynamic visualisation of OItilt and non-OItilt groups: a: systolic blood pressure (SBP); b: diastolic blood pressure (DBP); c: heart rate (HR); d: tissue saturation index (TSI). CI: confidence interval.

a: systolic blood pressure (SBP)

b: diastolic blood pressure (DBP)
c: heart rate (HR)

![Graph showing heart rate over time with error bars]

Error Bars: 95% CI

d: tissue saturation index (TSI)

![Graph showing tissue saturation index over time with error bars]

Error Bars: 95% CI
Logistic regression model with predictors of OI_{tilt}. OI_{tilt}: orthostatic intolerance during tilt; CFQ: Chalder Fatigue Scale; CES-D: Center for Epidemiological Studies Depression scale; cOH_{tilt}: classic orthostatic hypotension during tilt; POTS: postural orthostatic tachycardia syndrome; OR: odds ratio; CI: confidence interval.

| Predictor                        | OR    | 95% C.I. for OR | P     |
|----------------------------------|-------|----------------|-------|
| Age                              | 0.96  | 0.90 1.02      | 0.202 |
| Female sex                       | 2.99  | 0.71 12.65     | 0.136 |
| CFQ score                        | 0.97  | 0.86 1.08      | 0.547 |
| CES-D score                      | 1.02  | 0.97 1.08      | 0.435 |
| cOH_{tilt}                       | 1.04  | 0.28 3.79      | 0.955 |
| HR increase >30 bpm without OH_{tilt} | 0.15  | 0.01 1.53      | 0.109 |
| Lowest SBP after tilt            | 1.00  | 0.97 1.04      | 0.858 |