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Dysautonomia following COVID-19 is not associated with subjective limitations or symptoms but is associated with objective functional limitations



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BACKGROUND Individuals who contract coronavirus disease 2019 (COVID-19) can suffer with persistent and debilitating symptoms long after the initial acute illness. Heart rate (HR) profiles determined during cardiopulmonary exercise testing (CPET) and delivered as part of a post-COVID recovery service may provide insight into the presence and impact of dysautonomia on functional ability.

OBJECTIVE Using an active, working-age, post-COVID-19 population, the purpose of this study was to (1) determine and characterize any association between subjective symptoms and dysautonomia; and (2) identify objective exercise capacity differences between patients classified “with” and those “without” dysautonomia.

METHODS Patients referred to a post-COVID-19 service underwent comprehensive clinical assessment, including self-reported symptoms, CPET, and secondary care investigations when indicated. Resting HR >75 bpm, HR increase with exercise <89 bpm, and HR recovery <25 bpm 1 minute after exercise were used to define dysautonomia. Anonymized data were analyzed and associations with symptoms, and CPET outcomes were determined.

RESULTS Fifty-one of the 205 patients (25%) reviewed as part of this service evaluation had dysautonomia. There were no associations between symptoms or perceived functional limitation and dysautonomia ($P > .05$). Patients with dysautonomia demonstrated objective functional limitations with significantly reduced work rate (219 ± 37 W vs 253 ± 52 W; $P < .001$) and peak oxygen consumption ($\dot{V}O_2$: 30.6 ± 5.5 mL/kg/min vs 35.8 ± 7.6 mL/kg/min; $P < .001$); and a steeper (less efficient) $\dot{V}E/\dot{V}CO_2$ slope (29.9 ± 4.9 vs 27.7 ± 4.7 ; $P = .005$).

CONCLUSION Dysautonomia is associated with objective functional limitations but is not associated with subjective symptoms or limitation.

KEYWORDS Cardiopulmonary exercise testing; COVID-19; Dysautonomia; Exercise testing; Symptoms

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Introduction

With over 275 million confirmed cases,¹ severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a global crisis. In addition to the mortality burden, there is

the important secondary challenge of ongoing morbidity. A large proportion of patients experience symptoms for many months, even after mild initial infection.² Persistent debilitating symptoms include fatigue, breathlessness, muscle

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and/or joint pain, exercise intolerance, palpitations, headaches, memory loss, nausea, and dramatic mood disturbances.³ Several symptoms are impacted by the autonomic nervous system,⁴ with fatigue described as one of the major clinical features of dysautonomia in patients with coronavirus disease 2019 (COVID-19).⁵ Dysautonomia has been reported in other postviral illnesses.⁶ Establishing the frequency of dysautonomia and determining any association with symptoms and subjective or objective limitation in patients affected by COVID-19 is an essential step to understanding and managing this clinical entity.

Exercise provides a safe means to expose imbalances in parasympathetic and sympathetic activity that may be hidden at rest.⁷ Heart rate (HR) is recorded throughout a cardiopulmonary exercise test (CPET), and exercise HR profiles are prognostically important.⁸ Heart rate variability (HRV) (variability in the time interval between heart beats) recorded at rest is a well-validated marker of parasympathetic tone and is associated with the severity of acute COVID-19 illness.⁹

Most literature on the effects of COVID-19 focuses on severe acute illness, typically in vulnerable older adults with premonitory health conditions.¹⁰ The long-term effects of SARS-CoV-2 on individuals of working age in full-time employment are not known. In a military context, return to full military duty, including maximal exercise in hazardous remote environments, represents an important risk to personal health and operational effectiveness. Therefore, British Armed Forces personnel with severe acute COVID-19 illness or protracted symptoms (>12 weeks) attend a post-COVID-19 assessment clinic—the Defence Medical Services COVID-19 Recovery Service (DCRS).¹¹ Personnel who are medically downgraded due to COVID-19 are unable to deploy on operations and are not fit to return to active duty. Consequently, there is an operational and financial imperative to understand the impact of this virus on serving personnel. The results from this service are of direct relevance to wider public health. Using an active, working-age population, this study aims to (1) determine and characterize any association between subjective symptoms and dysautonomia; and (2) identify objective exercise capacity differences between patients classified “with” and those “without” dysautonomia in a population with enduring post-COVID-19 symptoms.

Methods

The post-COVID-19 clinic received patients referred from primary care with confirmed or probable COVID-19 infection, who met specific eligibility criteria (hospitalization, life-limiting symptoms beyond 12 weeks, desaturation $\leq 95\%$ on a Harvard step test, or chest pain with electrocardiographic [ECG] changes during acute illness).¹² In accordance with current policy on the use of clinical data for education, evaluation, and audit purposes, permission was granted for publication by the Defence Medical Rehabilitation Centre (DMRC) Caldicott Guardian and as such did not require formal ethical approval. The patient in-

formation and clinical data routinely collected in support of DCRS were used in this service evaluation. Data include the outcomes of every consecutive patient who attended the DCRS.

Demographics

Age, sex, height, body mass, and details of acute COVID-19 illness were recorded at the start of each admission.

Protocol

CPET

CPET was performed on an electromagnetically braked cycle ergometer (Lode Carnival, Lode BV, Groningen, The Netherlands) at 16° to 18°C, with indirect calorimetry (Metalyzer 3B, Cortex Biophysik, Leipzig, Germany). The CPET protocol followed at least 5 minutes of rest. Two-minute resting recording was followed by 2-minute unloaded cycling at a cadence of 60 rpm, before introduction of a 25-W resistance followed by a progressively increasing workload to volitional fatigue. Work rate/min ramp was selected to achieve 8 to 12 minutes of loaded exercise. Continuous measurement of ventilation (V_E), oxygen consumption (V_{O_2}), expired carbon dioxide (V_{CO_2}), HR, ECG, peripheral oxygen saturation (SpO_2), and workload were performed throughout the rest, exercise, and recovery phases.¹³ Maximal tests were defined by respiratory exchange ratio > 1.1 and/or ≥ 30 -second plateau in oxygen. Blood pressure, SpO_2 , rate of perceived exertion (RPE; 6–20 on Borg scale),¹⁴ and dyspnea (0–10 on modified Borg scale)¹⁵ were recorded every 2 minutes. Following attainment of maximal exercise capacity, participants remained stationary on the ergometer for at least 3 minutes.

Outcome measures

Spirometry

Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) were recorded.

Criteria for dysautonomia

Jouven's criteria were used for the diagnosis of exercise-associated dysautonomia⁸: (1) resting HR > 75 bpm; (2) increase in HR during exercise < 89 bpm; and (3) HR recovery < 25 bpm in the first 60 s after cessation of exercise. A diagnosis of dysautonomia required that all 3 criteria were met.

Symptoms

Symptoms with prevalence $> 25\%$ were carried forward for further analysis.

HRV

HRV values were obtained using 12-lead ECG acquisition during rest seated upright on the cycle ergometer. HRV also was obtained during the first 3 minutes of passive recovery after exercise. Both resting and recovery values have been

suggested as indicators of parasympathetic cardiac modulation.¹⁶

All individual raw data files containing R-R intervals were exported to Excel™ (Microsoft, Redmond, WA) before being read in Python. Automatic detection and removal of ectopic beats from the raw R-R intervals were performed using the method described by Acar et al,¹⁷ with the output inspected manually. Missing values were replaced using linear interpolation. Following preprocessing of the R-R intervals, the root square of the mean of squared differences of adjacent RR intervals (RMSSD), a measure of beat-to-beat variability,¹⁶ was calculated. RMSSD is the primary time-domain measure used to estimate the vagal-mediated changes reflected in HRV.¹⁸ RMSSD was measured at rest using the central 1-minute window of the 2-minute rest period. RMSSD was calculated in each 30-second window of the 3-minute recovery phase.^{19,20} All analysis was conducted using Python 3.7 (Python Software Foundation, Wilmington, DE).

Statistical analysis

The normality of all variables within the dataset was assessed using a Shapiro-Wilk test and inspection of the Q-Q plots, demonstrating normal distribution across most of variables. Given that the sample size was sufficiently large ($n = 205$), parametric tests were applied throughout.²¹ The most prevalent symptoms (prevalence $>25\%$) were extracted, and tests of associations between the classification of dysautonomia and each symptom were performed using χ^2 tests. To determine the effect of dysautonomia, independent sample t tests were conducted for CPET-related variables, identifying objective physiological differences between patients “with” and those “without” dysautonomia. For all statistical tests, an α threshold for significance of 0.05 was applied. All statistical analyses were performed using SPSS Version 27 (IBM, Armonk, NY).

Results

Mean duration from the onset of symptoms to the date of CPET assessment for the total cohort was 183 ± 77 days (~ 6 months). No significant differences in the duration between onset of symptoms and assessment date were observed between patients with and those without dysautonomia (180 ± 81 days vs 184 ± 76 days, respectively; $P = .347$).

Demographics

Of the 205 participants included in this study, 51 (25%) were classified with dysautonomia, according to the criteria outlined by Jouven et al⁸ (Figure 1). Intergroup analysis revealed patients with dysautonomia are older, have higher body mass index (BMI), and higher waist circumference. Body height and sex (84% men; 16% women) were comparable between groups (Table 1). Descriptive statistics of the HR parameters are given in Table 2.

Associations between symptoms of COVID-19 and dysautonomia

Fourteen of 38 symptoms had prevalence $>25\%$ and underwent associative testing. There were associations between low mood ($P = .007$), headaches ($P = .026$), and poor attention ($P = .047$) with the classification of dysautonomia. However, the effect sizes of these associations were all small (Cohen's $d = 0.190, 0.155, \text{ and } 0.139$, respectively). Results of each of the symptoms associative tests are given in Table 3.

Effect of dysautonomia on CPET outcomes

Notable differences in CPET findings were observed between patients who met the dysautonomia criteria⁸ and those who did not.

Spirometry

Although FVC (4.82 ± 0.79 L vs 5.17 ± 1.07 L; $P = .031$) and FEV₁ (3.63 ± 0.61 L vs 3.87 ± 0.75 L; $P = .036$) were lower in patients with dysautonomia, the magnitudes of difference were very small (Cohen's $d < 0.20$).

HR profile

Mean HR values were higher in patients with dysautonomia during rest (95 ± 12 bpm vs 81 ± 12 bpm; $P < .001$) and at the first ventilatory threshold (VT1) (114 ± 15 bpm vs 107 ± 17 bpm; $P = .017$) but less at peak exercise (170 ± 13 bpm vs 177 ± 15 bpm; $P = .003$). Increase in HR from rest to peak was lower in the dysautonomia group (75 ± 12 bpm vs 96 ± 13 bpm; $P < .001$). HR recovery at 1 minute following the cessation of exercise was also significantly less in patients with dysautonomia (17 ± 4 bpm vs 31 ± 17 bpm; $P < .001$).

HRV

HRV, measured by RMSSD, was lower in patients with dysautonomia (15 ± 9 m·s⁻¹ vs 29 ± 13 m·s⁻¹; $P < .001$), with a large effect size ($d = 1.057$). No difference was identified between groups for RMSSD measured during exercise recovery ($P > .05$).

Work rate (watts and lactate accumulation)

Work rate at VT1 (71 ± 16 W vs 80 ± 24 W; $P = .020$) and work rate at peak (219 ± 37 W vs 253 ± 52 W; $P < .001$) were lower in patients with dysautonomia. Despite the differences in work rate between groups, lactate accumulation at peak exercise was comparable.

Ventilation

Patients with dysautonomia had lower oxygen consumption (V_{O₂}) at VT1 (earlier anaerobic transition) (12.6 ± 2.1 mL/kg/min vs 14.1 ± 3.2 mL/kg/min; $P = .001$) and peak exercise (30.6 ± 5.5 mL/kg/min vs 35.8 ± 7.6 mL/kg/min; $P < .001$). This group also demonstrated lower values for V_{O₂} recorded at peak exercise (% predicted) ($107\% \pm 18\%$ vs $114\% \pm 20\%$; $P = .028$) (Figure 2B). Patients with dysautonomia demonstrated a greater percentage of their

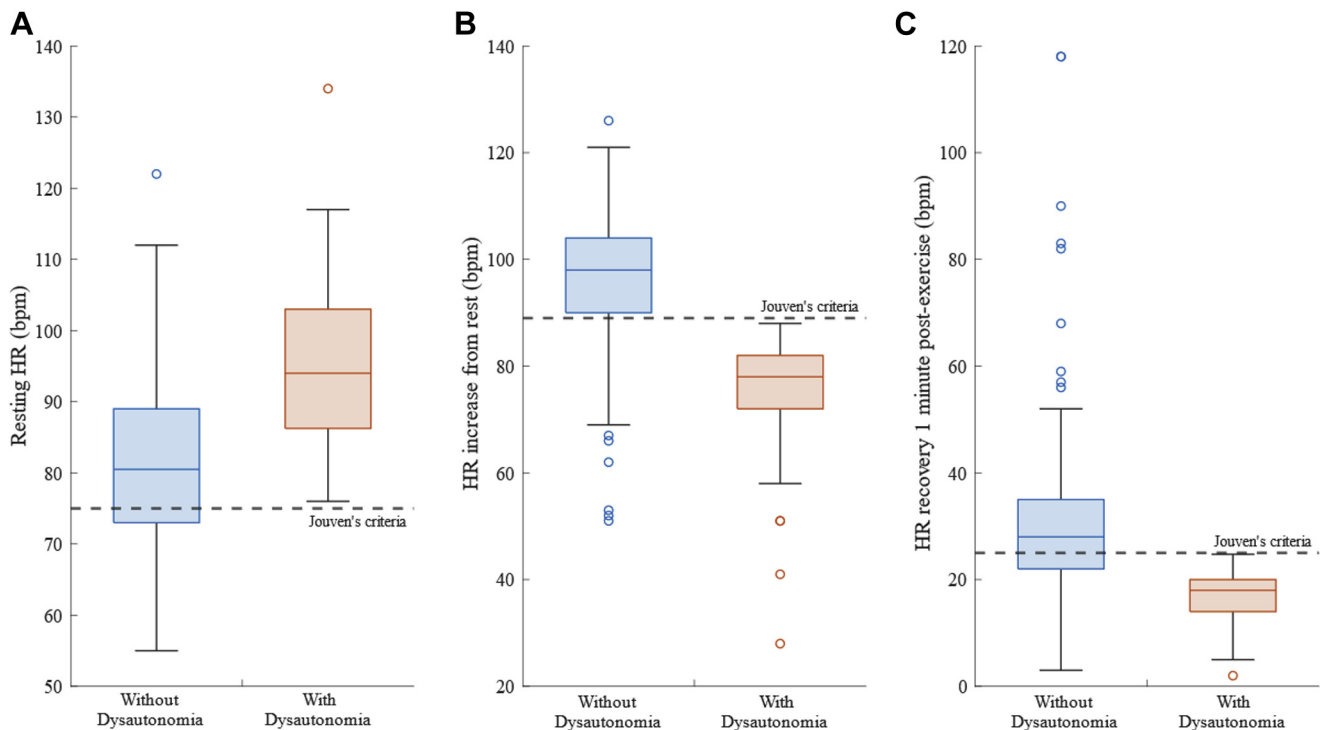


Figure 1 Boxplots showing between-group differences across each of the dysautonomia criteria specified in Jouven et al.⁸ **A:** Resting heart rate (HR). **B:** Heart rate increase from rest to peak stress. **C:** HR recovery 1 minute post-exercise.

predicted peak $\dot{V}O_2$ maximum at VT1 ($42\% \pm 6\%$ vs $40\% \pm 6\%$; $P = .047$), with small effect size ($d = 0.322$) (Figure 2A). No differences were observed in respiratory exchange ratio at peak exercise for patients with and those without dysautonomia (1.18 ± 0.05 vs 1.17 ± 0.05 , respectively; $P > .05$).

Patients with dysautonomia demonstrated lower ventilatory efficiency (higher $\dot{V}_E/\dot{V}CO_2$) at rest, VT1, and peak exercise. Furthermore, the $\dot{V}_E/\dot{V}CO_2$ slope was steeper (less efficient) in patients with dysautonomia vs those without dysautonomia (29.9 ± 4.9 vs 27.7 ± 4.7 , respectively; $P = .005$). Patients with dysautonomia demonstrated a higher breathing frequency at rest and at VT1 compared to those without dysautonomia.

No differences in breathing frequency at peak were demonstrated between groups ($P > .05$).

RPE and shortness of breath

Regarding perception of effort, RPE (rated 6–20) did not differ between groups during rest or at VT1; however, RPE at peak was significantly lower (indicating less perceived exertion) in patients with dysautonomia (16 ± 3 vs 17 ± 2 ; $P = .021$), and the effect size was small ($d = 0.378$). No differences in shortness of breath scores (rated 0–10) were demonstrated between patients with and those without dysautonomia during rest (0 ± 1 vs 0 ± 1 ; $P > .05$), at VT1 (1 ± 2 vs 1 ± 1 ; $P > .05$), or at peak exercise (6 ± 3 vs 7 ± 2 ; $P > .05$).

Table 1 Patient demographics

Variable	All patients (N = 205)	Without dysautonomia (n = 154)	With dysautonomia (n = 51)	Stat	P value	Effect size
Sex (M/F)	172/33	129/25	43/8	0.009 [†]	.927	0.006
Age (y)	38 ± 10	37 ± 10	43 ± 9	-4.053 [‡]	<.001*	0.655
Height (cm)	177 ± 8	177 ± 9	177 ± 7	0.443 [‡]	.658	0.072
Body mass (kg)	90 ± 17	89 ± 17	94 ± 16	-1.645 [‡]	.101	0.266
BMI (kg/m ²)	29 ± 4	28 ± 4	30 ± 4	-2.520 [‡]	.013*	0.407
Waist circumference (cm)	95 ± 13	94 ± 13	100 ± 12	-2.989 [‡]	.003*	0.500

Values are given as mean ± SD.

Effect size calculated using Cohen's d (small 0.2–0.5; medium 0.5–0.8; large >0.8). Significant P values * $P < .05$ and medium/large effect sizes are shown in bold.

BMI = body mass index.

[†] χ^2 statistic

[‡] t statistic.

Table 2 Physiological measures during the cardiopulmonary exercise testing protocol of all patients who attended the Defence Medical Services COVID-19 Recovery Service and differences between patients classified with and those without dysautonomia

Variable	All patients (n = 205)	Without dysautonomia (n = 154)	With dysautonomia (n = 51)	t	P value	Effect size
CPET						
V _{O₂} at rest (mL/kg/min)	5.1 ± 1.04	5.1 ± 1.1	5.2 ± 0.8	-0.454	.650	0.073
V _{O₂} at VT1 (mL/kg/min)	13.7 ± 3.0	14.1 ± 3.2	12.6 ± 2.1	3.273	.001 [†]	0.529
V _{O₂} at peak (mL/kg/min)	34.5 ± 7.4	35.8 ± 7.6	30.6 ± 5.5	4.544	<.001 [‡]	0.734
Work rate at VT1 (W)	78 ± 23	80 ± 24	71 ± 16	2.345	.020 [*]	0.379
Work rate at peak (W)	245 ± 51	253 ± 52	219 ± 37	4.329	<.001 [‡]	0.699
ΔV _{O₂} (L/min)/ΔWork (W)	10.7 ± 1.4	10.7 ± 1.4	10.7 ± 1.2	-0.008	.994	0.001
Lactate at rest (mmol/L)	1.3 ± 0.5	1.3 ± 0.5	1.5 ± 0.5	-3.254	.001 [†]	0.545
Lactate at peak (mmol/L)	12.7 ± 2.6	12.9 ± 2.6	12.2 ± 2.6	1.582	.115	0.280
O ₂ pulse	17.7 ± 4.4	17.9 ± 4.5	17.0 ± 3.9	1.264	.208	0.204
HR profile						
HR at rest (bpm)	84 ± 13	81 ± 12	95 ± 12	-7.343	<.001 [‡]	1.186
HR at VT1 (bpm)	109 ± 16	107 ± 17	114 ± 15	-2.408	.017 [*]	0.389
HR at peak (bpm)	175 ± 15	177 ± 15	170 ± 13	2.956	.003 [†]	0.478
Percent of predicted max HR	109 ± 8	109 ± 8	109 ± 8	-0.030	.976	0.005
HR recovery after 1 min (bpm)	27 ± 16	31 ± 17	17 ± 4	5.730	<.001 [‡]	0.926
HR increase from rest to peak (bpm)	91 ± 17	96 ± 13	75 ± 12	10.304	<.001 [‡]	1.665
HRV						
RMSSD at rest (m·s ⁻¹)	26 ± 14	29 ± 13	15 ± 9	6.243	<.001 [‡]	1.057
RMSSD (30–60 s recovery, m·s ⁻¹)	8 ± 10	8 ± 10	9 ± 10	-0.527	.599	0.089
RMSSD (90–120 s recovery, m·s ⁻¹)	9 ± 9	10 ± 10	7 ± 7	1.578	.116	0.267
RMSSD (150–180 s recovery, m·s ⁻¹)	9 ± 10	9 ± 9	10 ± 12	-1.013	.312	0.172
BP (mm Hg)						
Resting systolic BP (mm Hg)	121 ± 11	120 ± 10	121 ± 12	-0.735	.463	0.119
Resting diastolic BP (mm Hg)	81 ± 9	81 ± 9	82 ± 10	-0.682	.496	0.110
VT1 systolic BP (mm Hg)	140 ± 17	139 ± 17	141 ± 16	-0.464	.643	0.076
VT1 diastolic BP (mm Hg)	83 ± 12	82 ± 13	86 ± 9	-1.811	.072	0.295
Peak systolic BP (mmHg)	169 ± 21	169 ± 21	166 ± 22	1.056	.292	0.171
Peak diastolic BP (mmHg)	75 ± 22	73 ± 23	83 ± 16	-2.819	.005 [†]	0.455
Ventilation						
BF at rest (breaths/min)	16 ± 5	16 ± 4	18 ± 5	-2.756	.006 [†]	0.449
BF at VT1 (breaths/min)	20 ± 6	19 ± 5	23 ± 6	-3.609	<.001 [‡]	0.588
BF at peak (breaths/min)	47 ± 9	46 ± 9	48 ± 9	-1.234	.219	0.201
VE/V _{CO₂} at rest	30.2 ± 4.3	29.8 ± 4.3	31.3 ± 4.2	-2.107	.036 [*]	0.340
VE/V _{CO₂} at VT1	26.6 ± 3.4	26.1 ± 3.2	28.0 ± 3.7	-3.462	.001 [†]	0.559
VE/V _{CO₂} at peak	33.7 ± 7.7	32.7 ± 4.7	36.4 ± 12.9	-2.973	.003 [†]	0.480
VE/V _{CO₂} slope	28.3 ± 4.8	27.7 ± 4.7	29.9 ± 4.9	-2.839	.005 [†]	0.490
pcO ₂ rest	5.0 ± 0.6	5.0 ± 0.5	5.0 ± 0.8	0.037	.970	0.006
pcO ₂ peak	4.4 ± 0.8	4.4 ± 0.8	4.2 ± 0.6	1.191	.235	0.209

Values are given as mean ± SD unless otherwise indicated.

Effect size calculated using Cohen's *d* (small 0.2–0.5; medium 0.5–0.8; large >0.8).

Significant *P* values

BF = breathing frequency; BP = blood pressure; COVID-19 = coronavirus disease 2019; CPET = cardiopulmonary exercise testing; HR = heart rate; HRV = heart rate variability; RMSSD = root mean square of successive differences of R-R intervals; V_{CO₂} = expired carbon dioxide; V_E = ventilation; V_{O₂} = oxygen consumption; VT1 = first ventilatory threshold.

**P* < .05

†*P* < .01

‡*P* < .001 and medium/large effect sizes are shown in bold.

Discussion

This study identified dysautonomia in a significant proportion (25%) of active, working-age adults assessed at a median 6 months postacute COVID-19 illness. Using Jouven's criteria to identify those with dysautonomia occurring as part of a maximal exercise test,⁸ no clinically significant associations were found with subjective symptoms or exercise intolerance. However, objective functional capacity was reduced in dysautonomia.

In normal physiology, maximal exercise capacity is determined by circulatory limitation (cardiac output). Patients with dysautonomia are restricted in their ability to augment HR, from rest to peak stress, which reduces their capacity to increase peak cardiac output. The mean difference in HR response to exercise was 75 ± 12 bpm in patients with dysautonomia vs 96 ± 13 bpm in those without. This is despite a somewhat elevated resting HR in all groups (84 ± 13 bpm) that the authors conclude is primarily due to anticipatory

Table 3 Prevalence of symptoms in all patients, differences between patients with and those without dysautonomia, and associations between the presence of symptoms reported and dysautonomia

Symptom	All patients (N = 205)	Without dysautonomia (n = 154)	With dysautonomia (n = 51)	χ^2	P value	Effect size
Any SOB	61	58	69	1.67	.196	0.09
Moderate SOB	54	52	61	1.205	.272	0.077
Fatigue	54	51	60	1.386	.239	0.082
Any cognitive issues	48	48	47	0.015	.902	0.009
Poor concentration	40	40	41	0.039	.843	0.014
Mild SOB	37	34	45	2.121	.145	0.102
Staying asleep	32	25	31	0.714	.398	0.059
Muscle aches	31	30	33	0.216	.642	0.032
Poor memory	31	31	29	0.056	.814	0.016
Getting to sleep	28	25	37	2.688	.101	0.115
Low mood	28	23	43	7.374	.007[†]	0.19
Anxiety	26	26	28	0.043	.836	0.014
Headache	25	17	31	4.938	.026*	0.155
Poor attention	25	21	35	3.941	.047*	0.139

Values are given as % unless otherwise indicated.

Effect size calculated using Cohen's *d* (small 0.2–0.5; medium 0.5–0.8; large >0.8). Significant *P* values

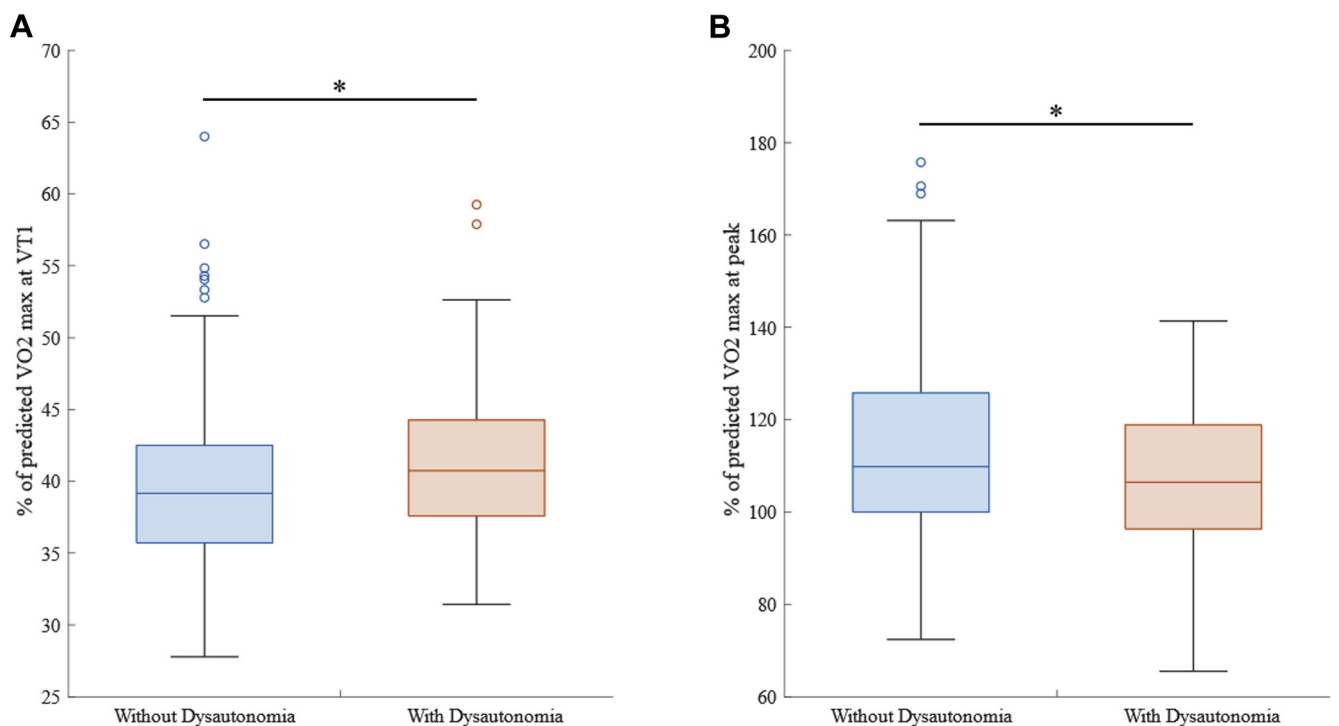
SOB = shortness of breath.

**P* < .05

[†]*P* < .01 are shown in bold.

HR response prior to a maximal exercise challenge. Although peak HR was lower in the group with dysautonomia, HR at VT1 was higher. Given that this is the point of transition to mixed aerobic and anaerobic metabolism, the higher HR may be implicated in reduced exercise capacity. Work rate at VT1 and peak exercise were significantly lower in patients with dysautonomia.

Unlike previous studies of chronic fatigue syndrome and postural orthostatic tachycardia syndrome, this study did not demonstrate an association between subjective limitation (symptoms and subjective exercise intolerance) and dysautonomia. Although there was an association between dysautonomia and the symptoms of headache, low mood, and poor attention, the effect sizes were very small. There was no

**Figure 2** Comparison of percentages of predicted maximum oxygen consumption (VO_{2max}) at VT1 (A) and actual VO_{2max} (B) between groups. Asterisk indicates significant between-group difference.

association with breathlessness, palpitations, or exertional intolerance, which might reasonably be anticipated to result from dysautonomia. During CPET, there were no differences in subjective symptoms of breathlessness at rest, VT1, or peak exercise, and the only differences in RPE values were demonstrated at peak RPE. The magnitude of this difference was trivial. These findings demonstrate that symptoms of post-COVID-19 syndrome are not predictive of dysautonomia. They also suggest that dysautonomia is unlikely to be a significant contributor to symptoms.

Measurement of HRV immediately following peak exercise did not reveal pathophysiological insights beyond the HR profiles used as an indirect measure of dysautonomia.⁸ Given the strong dependence of HRV on resting HR,²² this finding is perhaps unsurprising. The added benefit of utilizing HR recovery following maximal exercise in the indirect measure of dysautonomia⁸ was that HR recovery is a highly reproducible measure of an individual's vagal tone. It is independent of other physiological measures, including resting HR.⁷

There was a strong association between dysautonomia and lower ventilatory efficiency. \dot{V}_E/\dot{V}_{CO_2} values demonstrated impaired ventilatory efficiency at rest, VT1, and peak. Two contrasting mechanisms might explain this finding: (1) lung injury sufficient to cause ventilation/perfusion mismatch; and (2) inappropriate ventilation in excess of the body's physiological gas exchange requirements (hyperventilation). In this study, no association was identified between dysautonomia and lung pathology (computed tomographic scan and diffusing capacity) (for detailed results of clinical investigations, see the [Supplemental Appendix](#)). There also was no significant lowering of peak capillary P_{CO_2} in patients with vs those without dysautonomia to confirm inappropriate hyperventilation. However, patients with dysautonomia did demonstrate significantly higher breathing frequency at rest and VT1. It is possible that a central insult from this virus, with a recognized neurotropism,²³ might cause both dysautonomia and central abnormalities of ventilation.

Patients with dysautonomia demonstrate a less favorable body composition compared to those without dysautonomia (higher BMI and waist circumference). It is not possible to determine whether this reflects an increased risk of complex acute COVID-19 illness, the potential of post-COVID complications in those with a high BMI, or premorbid reduced cardiovascular fitness. Another possible factor is post-COVID debility reducing exercise capacity sufficiently to contribute to weight gain. Sex has previously been shown to be a risk factor for dysautonomia.²⁴ We identified no sex difference.

Study limitations

This was a comparatively large ($n = 205$) observational cohort study of a previously active, working-age population (currently underreported in the post-COVID literature) that found significant differences in autonomic function associated with reduced exercise capacity. However, there are

limitations to the study. The data are cross-sectional and do not determine whether patients are improving, or regressing symptomatically, with regard to HR responses and objective physical function. To determine whether abnormalities resolve over time, follow-up testing will be required. The data presented represent every consecutive patient who met the eligibility criteria and attended the DCRS. Comparisons to an unvaccinated or healthy control group were not possible. Although not used as a primary measure to identify dysautonomia, we recognize that HRV is frequently measured with patients in a supine position with controlled breathing strategies. Body postures have been shown to affect HRV recovery, with more upright postures slowing recovery.²⁵ Whereas resting HRV values were associated with dysautonomia, values recorded for 3 minutes of recovery were not. Only a few studies have performed test/retest reliability of HRV during postexercise recovery, and they have shown variable and inconsistent findings.¹⁶ Caution is advised when interpreting HRV measures calculated using very short epochs (eg, 30 seconds) during nonstationary conditions (particularly during the immediate postexercise recovery), as nonoscillatory changes in HR may contribute to HRV.¹⁶ Additional clinical information might be revealed by 24-hour HRV monitoring.⁹ Future research could tackle the question of whether blood or neuroradiology biomarkers of brain function are associated with dysautonomia in an effort to identify a mechanism for dysautonomia in this setting.

Conclusion

The prevalence of dysautonomia is high in this working-age, post-COVID-19 population. Dysautonomia is associated with objective functional limitation, but it is not associated with, or the cause of, subjective limitation or symptoms of cardiorespiratory disease.

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.hrthm.2021.12.005>.

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