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COVID-19 is getting on our nerves: sympathetic neural activity and haemodynamics in young adults recovering from SARS-CoV-2

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Key points

- The impact of SARS-CoV-2 infection on autonomic and cardiovascular function in otherwise healthy individuals is unknown.
- For the first time it is shown that young adults recovering from SARS-CoV-2 have elevated resting sympathetic activity, but similar heart rate and blood pressure, compared with control subjects.
- Survivors of SARS-CoV-2 also exhibit similar sympathetic nerve activity and haemodynamics, but decreased pain perception, during a cold pressor test compared with healthy controls.
- Further, these individuals display higher sympathetic nerve activity throughout an orthostatic challenge, as well as an exaggerated heart rate response to orthostasis.
- If similar autonomic dysregulation, like that found here in young individuals, is present in older adults following SARS-CoV-2 infection, there may be substantial adverse implications for cardiovascular health.

Abstract The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can elicit systemic adverse physiological effects. However, the impact of SARS-CoV-2 on autonomic and cardiovascular function in otherwise healthy individuals remains unclear. Young adults who tested positive for SARS-CoV-2 (COV+; n = 16, 8 F) visited the laboratory 35 ± 16 days following diagnosis. Muscle sympathetic nerve activity (MSNA), systolic (SBP) and diastolic (DBP) blood pressure, and heart rate (HR) were measured in participants at rest and during a 2 min cold pressor test (CPT) and 5 min each at 30° and 60° head-up tilt (HUT). Data were compared with age-matched healthy controls (CON; n = 14, 9 F). COV+ participants (18.2 ± 6.6 bursts min^{-1}) had higher resting MSNA burst frequency compared with CON (12.7 ± 3.4 bursts min^{-1}) (P = 0.020), as well as higher MSNA burst incidence and total activity. Resting HR, SBP and DBP were not different. During CPT, there were no differences in MSNA, HR, SBP or DBP between groups. COV+ participants reported less pain during the CPT compared with CON (5.7 ± 1.8 *vs.* 7.2 ± 1.9 a.u., P = 0.036). MSNA was higher in COV+ compared with CON during HUT. There was a group-by-position interaction in

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MSNA burst incidence, as well as HR, in response to HUT. These results indicate resting sympathetic activity, but not HR or BP, may be elevated following SARS-CoV-2 infection. Further, cardiovascular and perceptual responses to physiological stress may be altered, including both exaggerated (orthostasis) and suppressed (pain perception) responses, compared with healthy young adults.

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Introduction

The novel coronavirus disease of 2019 (COVID-19) pandemic has resulted in over 2 million deaths worldwide, but tens of millions of people have survived the disease. Survivors of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exhibit a range of symptoms, indicating the systemic potential of the virus (Chen *et al.* 2020). Widespread decrements in physiological function could be explained, in part, by the functional host receptor of SARS-CoV-2, angiotensin-converting enzyme-2 (ACE2), which is present in epithelial cells of the heart, lungs, blood vessels, kidneys, liver and gastrointestinal tract endothelium (Bourgonje *et al.* 2020; Monteil *et al.* 2020). Accordingly, recent findings indicate individuals with SARS-CoV-2 experience myocarditis, hepatic dysfunction and gastrointestinal symptoms, including nausea, vomiting and abdominal pain (Ferm *et al.* 2020; Jothimani *et al.* 2020; Siripanthong *et al.* 2020). Further, our group has observed that infection with SARS-CoV-2 has detrimental effects on the vasculature in healthy young adults, evidenced by significant decreases in flow-mediated dilatation and response to single passive limb movement, as well as higher arterial stiffness when compared with healthy controls (Ratchford *et al.* 2021).

SARS-CoV-2 infection is also associated with inflammatory cytokine storms, which can have sweeping implications for the respiratory system, vasculature and nervous system (Paybast *et al.* 2020). While inflammatory cytokine storms can be life-threatening, even relatively mild increases in inflammatory biomarkers result in oxidative stress (Tank *et al.* 2011; Moreira *et al.* 2017). These proinflammatory mediators can subsequently cross the blood–brain barrier, ultimately increasing activation of the sympathetic nervous system (SNS) (Pongratz & Straub, 2014). The SNS is integral to optimal regulation of the cardiovascular system (Macefield, 2013), and altered sympathetic neural activity is associated with disease risk (Vallbo *et al.* 2004; Barretto *et al.* 2009; Malpas, 2010). Increases in resting and reactive sympathetic activity can have detrimental effects on several physiological systems, including alterations in cardiac contraction (Moreira *et al.* 2017), impairments in vascular function (Thijssen *et al.* 2006) and reductions in exercising blood flow capacity (Stuckless & Pyke, 2015); accordingly, sympathetic overdrive has been identified as an independent predictor of mortality in a number of diseases (Grassi *et al.* 1995, 2015; Brunner-La Rocca *et al.* 2001; Huggett *et al.* 2003; Taylor *et al.* 2014; Holwerda *et al.* 2019).

Individuals with underlying cardiometabolic diseases such as hypertension, diabetes and obesity typically experience heightened sympathetic tone, which may be exacerbated by acute infection such as SARS-CoV-2. However, even healthy individuals can be adversely impacted by the virus; recent work has suggested that ∼30% of otherwise healthy individuals who were diagnosed and experienced mild SARS-CoV-2 symptoms report long-term decrements to their overall health (Tenforde *et al.* 2020), including autonomic dysfunction (Gozalbo-Rovira *et al.* 2020; Ponti *et al.* 2020). Individuals diagnosed with SARS-CoV-2 show significant increases in proinflammatory cytokines (Wu *et al.* 2020), which can impact sympathetic outflow. However, direct measures of sympathetic nerve activity, assessed simultaneously with haemodynamic parameters, have yet to be examined in individuals recovering from SARS-CoV-2 infection.

Thus, the purpose of the current study was to investigate autonomic (dys)function and haemodynamics in otherwise healthy young adults recently infected with SARS-CoV-2. Utilizing a cross-sectional study design, we compared young adults who recently tested positive for SARS-CoV-2 with young healthy adults as a control group. We hypothesized that participants recovering from SARS-CoV-2 infection would exhibit higher resting and reactivity measures of muscle sympathetic nerve activity (MSNA), heart rate (HR) and blood pressure (BP), when compared with healthy controls.

Methods

Ethical approval

All participants were informed of the study purpose and protocols, and they gave written informed consent to

protocols, approved by the Institutional Review Board of Appalachian State University (nos 16-0208, 16-0335 and 20-0304). The study was performed in accordance with the ethical standards described by the *Declaration of Helsinki*.

Study design

Otherwise healthy young adults who tested positive for SARS-CoV-2 using a nasopharyngeal swab polymerase chain reaction (PCR) assay reported to the laboratory 3–8 weeks following their positive test (COV+). Control subjects (CON) were studied between 15 February 2017 and 25 February 2020; these dates are prior to the first confirmed case of COVID-19 in North Carolina, USA (3 March 2020). Control subjects did not report any flu-like symptoms. All participants were free from cardiovascular, metabolic or renal disease, and female participants were not currently pregnant or breastfeeding. COV+ participants did not require hospitalization during or following infection.

COV+ participants completed an in-house COVID-19 symptom severity survey on the day of testing (Fig. 1). On a scale of 0–100 of increasing severity, participants subjectively rated the severity of 18 symptoms typically associated with COVID-19: chest pain, chills, diarrhoea, dizziness or vertigo, dry cough, dry eyes, dry mouth, fatigue, fever over 37.9°C, headache, lack of appetite, loss of smell or taste (anosmia), muscle or body aches, nasal congestion or runny nose, nausea or vomiting, shortness of breath (dyspnoea), sore joints, and sore throat.

For testing, participants arrived at the laboratory in a fasted state, having abstained from exercise, caffeine and alcohol for at least 24 h before testing, and $\geq$4 h after a snack or light meal. Testing took place in a quiet, environmentally controlled laboratory, with an ambient temperature of $\sim$23°C.

Experimental measures

Participants were in the supine position on a bed for instrumentation. Multiunit MSNA was assessed using the microneurographic technique, as previously described (Wallin *et al.* 1974; Vallbo *et al.* 1979; White *et al.* 2015). Briefly, a recording electrode was inserted in the peroneal nerve at the fibular head, and a reference electrode was inserted subcutaneously 2–3 cm from the recording electrode. The nerve signals were amplified (70,000–160,000-fold), band-pass filtered (700–2000 Hz), full-wave rectified, and integrated with a resistance–capacitance circuit (time constant 0.1 s). Criteria for adequate MSNA recording included (a) pulse synchrony, (b) increases in response to breath-holding, and (c) insensitivity to gentle skin touch or a loud noise.

HR determined from lead II of the electrocardiogram (Biopac Systems, Goleta, CA, USA), beat-by-beat BP measured by finger photoplethysmography (NOVA, Finapres Medical Systems, Enschede, The Netherlands) and MSNA (662C-4, Department of Biomedical Engineering, University of Iowa, Iowa City, IA, USA) were continuously recorded during all tests. Arm cuff systolic (SBP) and diastolic (DBP) pressures were measured by electrosphygmomanometry (NOVA, Finapres Medical Systems) at specified time points during each test.

After an acceptable nerve recording site had been found and following 10 min of supine rest, baseline data were collected during spontaneous breathing for 5 min. The subject then performed a cold pressor test (CPT), where the hand was immersed in an ice water bath for 2 min. Participants were instructed to avoid breath holding during the test. After the test, the subject's hand was immediately dried and wrapped in warmed towels during a 3 min period of recovery. The CPT was used to assess the central integration of vasomotor sympathetic processes and their efferent pathways (Victor *et al.* 1987; Seals, 1990). Immediately following recovery from the CPT, participants were asked to rate their perception of pain on a numeric rating scale of 1–10, with 1 being no pain and 10 being the worst pain imaginable (Serlin *et al.* 1995; Bijur *et al.* 2003).

When the subject's HR and BP were within 5 beats min^{-1} and 5 mmHg from baseline values they were subsequently tilted passively to 30° and 60° head-up tilt (HUT) for 5 min each. A belt was placed across the participant's waist to ensure that they would not fall. A bicycle saddle was used to support approximately two-thirds of the subject's body weight during tilt; thus, when the subject stood on a plate at the end of the tilt bed on one leg, the other leg was able to be relaxed for microneurography.

Data analysis

Scores for each subject on the COVID-19 symptom severity survey were calculated as (a) the total severity (i.e. sum of scores across the 18 possible symptoms), and (b) the average of existing symptoms (i.e. total severity divided by number of symptoms).

Sympathetic and haemodynamic data were sampled at 625 Hz with a commercial data acquisition system (Biopac Systems). MSNA bursts were identified using computer software (LabView Software; National Instruments, Austin, TX, USA) with a 3:1 signal-to-noise ratio threshold within a 0.5 s search window and an expected burst reflex latency of 1.3 s from the preceding R-wave (Cui *et al.* 2001). All bursts were confirmed by an

experienced microneurographer, and re-running of the data with sound (to listen for sympathetic bursts from the raw signal) was performed using Spike2 8.08 software (Cambridge Electronic Design, Cambridge, UK) to confirm any questionable bursts. Within the integrated neurogram, the burst with the largest amplitude during baseline was assigned a value of 100, and all bursts in that trial (e.g. spontaneous breathing, baseline prior to CPT)

COVID-19 Severity Survey
For Research Purposes Only

Date: _____ ID Code: _____
To be filled out by research team ONLY.

Write down your score 0 to 100 how severe your COVID-19 symptoms are today.
Use only whole numbers to indicate your score for each symptom.

Symptom	**N/A**	**Mild**				**Moderate**					**Severe**
	0	10	20	30	40	50	60	70	80	90	100

Chest Pain _____ Score: _____

Chills _____ Score: _____

Diarrhea _____ Score: _____

Dizziness/Vertigo _____ Score: _____

Dry Cough _____ Score: _____

Dry Eyes _____ Score: _____

Dry Mouth _____ Score: _____

Fatigue _____ Score: _____

Fever, over 100.3ºF _____ Score: _____

Headache _____ Score: _____

Lack of Appetite _____ Score: _____

Loss of Smell/Taste, Anosmia _____ Score: _____

Muscle or Body Aches _____ Score: _____

Nasal Congestion or Runny Nose _____ Score: _____

Nausea or Vomiting _____ Score: _____

Shortness of Breath, Difficulty Breathing, Dyspnea _____ Score: _____

Sore Joints _____ Score: _____

Sore Throat _____ Score: _____

Other: _____ (Describe Symptom) _____ Score: _____

Other: _____ (Describe Symptom) _____ Score: _____

Other: _____ (Describe Symptom) _____ Score: _____

To be filled out by research team ONLY.

Number of Symptoms: _____ Symptom Severity Total: _____ Average Symptom Severity: _____

Figure 1. COVID-19 symptom severity survey

were normalized to that burst (Joyner & Halliwill, 2000). In this same manner, calibration bursts were assigned during the baseline periods preceding each test (i.e. CPT, HUT). Burst areas of the integrated neurogram, systolic and diastolic pressures, and R–R interval were measured simultaneously on a beat-to-beat basis. Total activity of the burst was defined as the burst area of the rectified and integrated neurogram. The number of bursts per minute (burst frequency) and per 100 heartbeats (burst incidence) and total burst area per minute (total activity) were used as quantitative indices of MSNA. Continuously recorded variables (i.e. MSNA, HR, beat-by-beat BP) were averaged over the 5 min period during rest, as well as over each 5 min period during HUT. These variables were averaged over 1 min baseline periods prior to CPT and HUT, each 30 s period during CPT and each minute during recovery from CPT. Arm cuff BP was measured at the following time points: minutes 1 and 4 of rest; once during baseline prior to and each minute during the CPT, and at 90 s into the subsequent recovery; and minutes 1 and 4 of each 30° and 60° HUT. Pressures were averaged during rest.

Sympathetic transduction at rest was calculated using an open-source program and instructions that were recently published (O'Brien *et al.* 2021). Briefly, electrocardiogram, arterial pressure and MSNA signals (i.e. burst/no burst) from the 5 min resting period were time aligned; the absolute (mmHg) and relative (%) changes (Δ) in mean arterial pressure (MAP) were then determined for each of 12 consecutive cardiac cycles following an MSNA burst (change calculated from the cardiac cycle in which the burst occurred). The average ΔMAP was determined for each cardiac cycle, and the largest value was used as the measure of sympathetic transduction. Similarly, pressor responses following 'non-bursts' (i.e. cardiac cycles absent of MSNA bursts; sympathetic quiescence) were determined by tracking ΔMAP for 12 cardiac cycles following a non-bursting cardiac cycle. The average ΔMAP was determined for each cardiac cycle, and the nadir change was used as the measure of the pressor response to non-bursts.

Due to difficulties maintaining the MSNA signal in all participants during HUT, short-term heart rate variability (HRV) was also assessed as an index of autonomic function using lead II of the electrocardiogram during tilting. AcqKnowledge 4.4 software (Biopac Systems) was utilized to perform HRV analysis of R–R intervals for the frequency and time domains. The frequency-domain indices included low frequency (LF; 0.04–0.15 Hz; in ms and normalized units (n.u.) = LF/(LF + HF) × 100) and high frequency (HF; 0.15–0.4 Hz; in ms and n.u.) power, and the ratio of LF to HF (LF/HF). The time-domain indices included root mean square of successive differences between heart beats (RMSSD) and proportion of total R–R intervals exceeding 50 ms (pNN50).

Statistical analysis

Statistical analysis was performed using commercially available software (IBM SPSS Statistics Version 26, IBM Corp., Armonk, NY, USA; SAS Version 9.4, SAS Institute, Cary, NC, USA). While MSNA has not been measured in SARS-CoV-2, nor in infections similar to SARS-CoV-2, an *a priori* power analysis ($\alpha = 0.05$, $1 - \beta = 0.8$) based on heart rate variability data following Influenza A (H1N1) infection (Mattei *et al.* 2011) was performed using G*Power version 3.0.10 to determine minimum sample size. A two-tailed Student's *t*-test for independent samples was performed to examine differences between groups for subject characteristics, resting outcome measures and peak changes in outcome measures during stress. Pearson's bivariate correlations were utilized to examine relationships between outcome variables. Two-way repeated-measures analysis of variance (ANOVA) was performed to assess differences between groups in responses to the CPT (group × time) and HUT (group × body position) tests. Linear mixed models were used to assess main effects of position (BL, 30° and 60° HUT, recovery), group (COV+, CON) and group-by-position interactions for measures of MSNA during HUT. Sidak's *post hoc* analysis was conducted when interactions were identified. Levene's test was used to assess the equality of variances and the Shapiro–Wilk test to assess normality of data. Statistical significance was set at $P < 0.05$. Data are expressed as means ± standard deviation (SD).

Results

Control (CON; $n = 14$, 9 F) and experimental (COV+; $n = 16$, 8 F) participants had similar demographic and anthropometric characteristics ($P > 0.05$, Table 1). All participants in each group were either sedentary or recreationally active, performing <150 min week^{-1} of aerobic exercise. Eight CON and seven COV+ participants were taking oral contraceptives; participants otherwise were taking no medications. One COV+ participant was asymptomatic, while all other COV+ participants reported having only mild flu-like symptoms. Testing for COV+ participants took place an average of 35 ± 16 days following a positive SARS-CoV-2 PCR test result.

SARS-CoV-2 symptom severity

The average symptom score on the SARS-CoV-2 Symptom Severity Survey was 19 a.u. (out of a possible

Table 1. Subject characteristics

Characteristic	CON (n = 14, 9 F)	COV+ (n = 16, 8 F)	P
Age (years)	21.4 ± 3.3	20.4 ± 1.2	0.277
Height (cm)	171 ± 8	173 ± 10	0.652
Body mass (kg)	74 ± 11	71 ± 13	0.490
Body mass index (kg m^{-2})	25.1 ± 3.5	23.8 ± 2.9	0.254

Data are means ± SD. CON, control group; COV+, COVID group. Independent samples t-tests were used to compare characteristics.

Table 2. Reported symptoms from symptom severity survey

Symptom	n	COV+ symptom score (a.u.) (n = 16)
Chest pain	2	20 ± 14
Diarrhoea	1	50
Dizziness/vertigo	2	9 ± 2
Dry cough	5	16 ± 15
Dry eyes	2	15 ± 7
Dry mouth	2	13 ± 4
Fatigue	6	20 ± 9
Fever, over 37.94°C	0	0
Headache	2	30 ± 14
Lack of appetite	2	25 ± 21
Anosmia	6	43 ± 33
Muscle or body aches	4	8 ± 3
Nasal congestion or runny nose	6	18 ± 20
Nausea or vomiting	1	50
Shortness of breath, difficulty breathing, dyspnoea	5	18 ± 19
Sore joints	1	20
Sore throat	4	16 ± 6

Data are means ± SD. a.u., arbitrary units out of 100; COV+, COVID group.

100 a.u., Table 2). Participants reported experiencing an average of 3.3 ± 2.2 symptoms at time of testing. The symptoms with the highest ratings on the day of testing were anosmia (n = 6, rating = 43 ± 33 a.u.), fatigue (n = 6, rating = 20 ± 8 a.u.) and nasal congestion (n = 6, rating = 18 ± 20 a.u.). Total severity score (i.e. sum of scores across the 18 possible symptoms) was significantly positively correlated with resting HR (r = 0.50, P = 0.048). Symptom severity scores and subscales were not related to any other physiological outcome measure.

Resting sympathetic activity and haemodynamics

Resting MSNA data are displayed in Fig. 2. MSNA was not obtained in four of the COV+ participants. COV+ (n = 12, 4 F; 18.2 ± 6.6 bursts min^{-1}; males (M): 17.4 ± 6.1 bursts min^{-1}; females (F): 19.8 ± 8.4 bursts min^{-1}) had higher resting MSNA burst frequency compared with CON (n = 14, 9 F; 12.7 ± 3.4 bursts min^{-1}; M: 12.6 ± 1.9 bursts min^{-1}; F: 12.8 ± 4.1 bursts min^{-1}) (P = 0.020). Similarly, resting MSNA burst incidence (COV+ 29.9 ± 11.4 bursts 100 heart beats^{-1}; CON: 19.8 ± 5.3 bursts 100 heart beats^{-1}; P = 0.013) and total activity (COV+: 285 ± 101 a.u. min^{-1}; CON: 159 ± 46 a.u. min^{-1}; P = 0.001) were greater in COV+ compared with CON. However, resting HR (COV+: 63 ± 9 beats min^{-1}; CON: 65 ± 9 beats min^{-1}; P = 0.435), SBP (COV+: 132 ± 10 mmHg; CON: 129 ± 13 mmHg; P = 0.399) and DBP (COV+: 78 ± 4 mmHg; CON: 75 ± 8 mmHg; P = 0.157) were not different between groups. There were no correlations between any quantitative indices of resting MSNA and BP (P = 0.730–0.997).

Resting absolute (COV+: 1.91 ± 1.38 mmHg; CON: 1.11 ± 0.78 mmHg; P = 0.077) and relative (COV+: 2.23 ± 1.32%; CON: 1.39 ± 0.82%; P = 0.059) measures of sympathetic transduction to blood pressure were not significantly different between groups. However, the absolute (COV+: −1.11 ± 1.09 mmHg; CON: −2.49 ± 1.39 mmHg; P = 0.010) and relative (COV+: −1.13 ± 0.84%; CON: −1.99 ± 1.00%; P = 0.028) decreases in MAP following 'non-bursts' were significantly less in COV+ compared with CON.

Table 3. Haemodynamic responses to the cold pressor test

Variable	BL	CPT0.5	CPT1.0	CPT1.5	CPT2.0	REC1	REC2	REC3
HR (beats min^{-1})								
CON	67 ± 11	75 ± 12	77 ± 15	77 ± 14	73 ± 14	70 ± 12	64 ± 9	64 ± 8
COV+	64 ± 12	70 ± 13	74 ±16	72 ± 14	77 ± 33	69 ±27	62 ±8	61 ± 10
SBP (cuff; mmHg)								
CON	134 ± 11		143 ± 16		148 ± 13		134 ± 10	
COV+	135 ± 11		151 ± 16		153 ± 13		136 ± 10	
DBP (cuff; mmHg)								
CON	80 ± 9		92 ± 11		93 ± 11		80 ± 5	
COV+	81 ± 6		92 ± 8		94 ± 8		78 ± 5	

Data are means ± SD. HR data averaged over 1 min at BL, every 0.5 min during CPT, and each minute during the 3 min of REC. SBP and DBP taken once during BL and REC and once every minute during CPT. Two-way repeated measures ANOVA was used to compare groups over the CPT. HR, time effect $P = 0.001$, group effect $P = 0.627$, time × group interaction $P = 0.566$; SBP, time effect $P < 0.001$, group effect $P = 0.734$, time × group interaction $P = 0.487$; DBP, time effect $P < 0.001$, group effect $P = 0.990$, time × group interaction $P = 0.750$. BL, baseline; CON, control group; CPT, cold pressor test; COV+, COVID group; DBP, diastolic blood pressure; HR, heart rate; REC, recovery; SBP; systolic blood pressure.

Responses to cold pressor test

There was a main effect of group on MSNA burst incidence (COV+: 35.4 ± 3.2 bursts 100 heart beats^{-1}; CON: 24.7 ± 3.1 bursts 100 heart beats^{-1}; $P = 0.028$), but not burst frequency ($P = 0.097$) or total MSNA ($P = 0.244$), during the CPT (Fig. 3*A*). Group-by-time analyses indicate MSNA burst frequency ($P = 0.245$), incidence ($P = 0.180$) and total MSNA ($P = 0.587$) (Fig. 3*B*) responses to the CPT were not significantly different between groups.

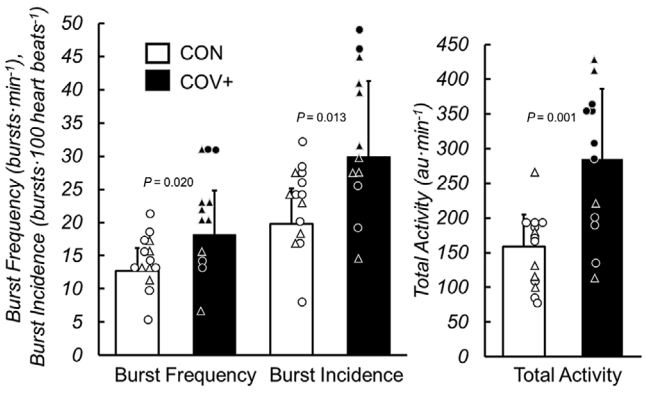

Figure 2. Resting muscle sympathetic nerve activity (MSNA) burst frequency, burst incidence and total activity in control subjects (CON) and subjects who tested positive for SARS-CoV-2 (COV+)
Two-tailed Student's *t*-tests for two samples of unequal variance were performed between CON (white bars, $n = 14$) and COV+ (black bars, $n = 12$) groups. COV+ participants had significantly higher resting burst frequency ($P = 0.020$), burst incidence ($P = 0.013$) and total activity ($P = 0.001$) compared with CON. Individual data are presented as triangles (male subjects) and circles (female subjects). Data are means ± SD.

There were also no differences in HR, SBP or DBP or the responses of these variables between groups during the CPT (Table 3).

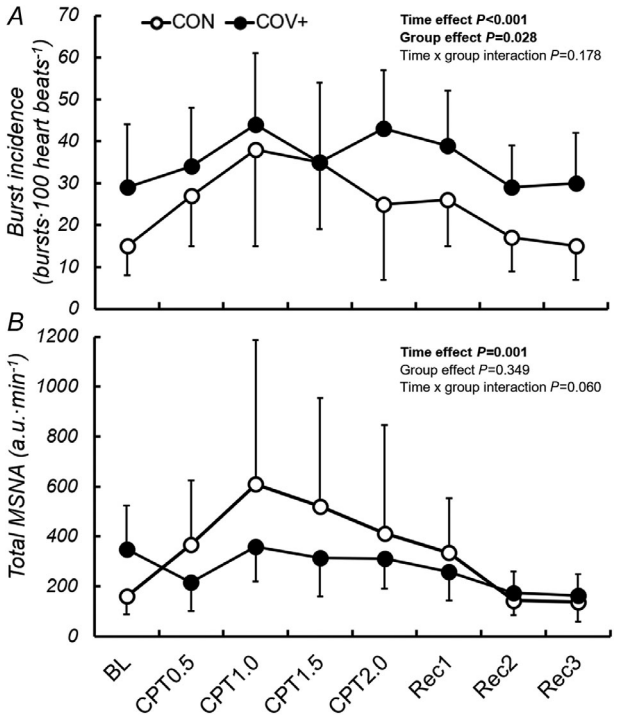

Figure 3. Muscle sympathetic nerve activity (MSNA) burst incidence (*A*) and total activity (*B*) during baseline before (BL), every 30 s during, and each minute of recovery from the cold pressor test in control subjects (CON) and subjects who tested positive for SARS-CoV-2 (COV+)
Two-way repeated measures ANOVA (group-by-time) were performed between CON (open circles, $n = 12$) and COV+ (filled circles, $n = 11$). Data are means ± SD.

COV+ participants reported lower ratings of pain during the CPT compared with CON (5.7 ± 1.8 *vs.* 7.2 ± 1.9 a.u., $P = 0.036$). The correlation between pain ratings and change in total MSNA during the CPT was $r = 0.355$ ($P = 0.081$).

Responses to orthostatic challenge

MSNA recordings during the orthostatic challenge were achieved on a subset of participants (COV+: $n = 7$, 2 F for 30° HUT, and $n = 4$, 1 F for 60° HUT; CON: $n = 7$, 4 F for both 30° and 60° HUT) (Fig. 4). Body position (i.e. baseline, 30° and 60° HUT) significantly affected MSNA burst frequency ($P < 0.001$), incidence ($P < 0.001$) and total activity ($P < 0.001$). MSNA burst frequency (main effect of group, $P = 0.007$), incidence ($P = 0.003$) and total activity ($P = 0.019$) were significantly higher in COV+ compared with CON during the orthostatic challenge. Further, there was a significant group-by-position interaction in burst incidence ($P = 0.012$), but not in burst frequency ($P = 0.234$) or total activity ($P = 0.967$). The change in MSNA burst incidence from baseline to 30° HUT was +4.1 ± 9.8 bursts 100 heart beats^{-1} in COV+ and +12.9 ± 5.5 bursts 100 heart beats^{-1} in CON ($P = 0.068$), while the change from baseline to 60° HUT was +2.0 ± 13.6 bursts 100 heart beats^{-1} in COV+ and +16.7 ± 5.5 bursts 100 heart beats^{-1} in CON ($P = 0.042$).

Indices of HRV during HUT can be found in Table 4. There were significant main effects of body position on RMSSD ($P < 0.001$), pNN50 ($P < 0.001$), LF (n.u.) ($P < 0.001$), HF (ms) ($P = 0.002$), HF (n.u.) ($P < 0.001$)

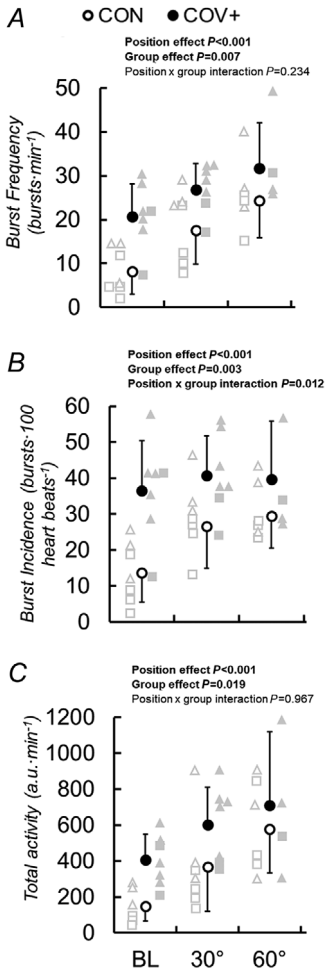

Figure 4. MSNA burst frequency (*A*), incidence (*B*) and total activity (*C*) before (BL) and during 5 min each at 30° and 60° head-up tilt (HUT) in a subset of control subjects (CON, *n* = 7, 4 F for both 30° and 60° HUT) and subjects who tested positive for SARS-CoV-2 (COV+, *n* = 6, 1 F for 30° HUT, and *n* = 4, 1 F for 60° HUT)

Linear mixed model analysis was performed to assess differences in MSNA between CON (means presented as open circles) and COV+ (means presented as filled circles) during HUT. Individual data are presented as triangles (male subjects) and squares (female subjects). Data are means ± SD.

Table 4. Indices of heart rate variability during orthostatic challenge

Variable	BL	30° HUT	60° HUT	*P* for interaction
RMSSD (ms)				
CON	54 ± 17	42 ± 15	25 ± 4	
COV+	101 ± 65	58 ± 30	34 ± 12	0.049
pNN50 (%)				
CON	31 ± 17	17 ± 8	5 ± 3	
COV+	47 ± 26	31 ± 21	10 ± 9	0.364
LF (ms^2)				
CON	195 ± 142	177 ± 148	169 ± 131	
COV+	269 ± 233	220 ± 192	248 ± 190	0.900
LF (n.u.)				
CON	54 ± 12	59 ± 17	73 ± 18	
COV+	39 ± 15	58 ± 23	81 ± 11	0.005
HF (ms^2)				
CON	150 ± 88	106 ± 77	43 ± 24	
COV+	648 ± 735	225 ± 248	49 ± 35	0.026
HF (n.u.)				
CON	46 ± 12	40 ± 16	27 ± 18	
COV+	61 ± 15	42 ± 23	19 ± 11	0.004
LF/HF				
CON	1.3 ± 0.5	2.1 ± 1.5	4.7 ± 3.9	
COV+	0.7 ± 0.4	2.4 ± 2.2	6.6 ± 4.7	0.214

Data are means ± SD. RMSSD ($P = 0.011$), pNN50 ($P = 0.016$) and HF (ms) ($P = 0.024$) were significantly different between groups. 30° HUT, 30 degree head-up tilt; 60° HUT, 60 degree head-up tilt; BL, baseline; CON, control subjects; COV+, SARS-CoV-2 subjects; HF, high frequency power(0.15–0.4 Hz; in ms and n.u.); LF, low frequency power (0.04–0.15 Hz; in ms and normalized units (n.u.) = LF/(LF + HF) × 100); pNN50, proportion of R–R intervals >50 ms; REC, recovery; RMSSD, root mean square successive differences.

and LF/HF ratio ($P < 0.001$). RMSSD ($P = 0.011$), pNN50 ($P = 0.016$) and HF (ms) ($P = 0.024$) were also significantly different between groups, with COV+ displaying higher values compared with CON. There were significant group-by-position interactions in RMSSD ($P = 0.046$), LF (n.u.) ($P = 0.005$), HF (ms) ($P = 0.024$) and HF (n.u.) ($P = 0.004$). However, LF/HF ratio in response to the orthostatic challenge was similar between groups ($P = 0.213$).

There were also significant effects of body position (i.e. baseline, 30° and 60° HUT) on HR ($P < 0.001$) and DBP ($P = 0.001$), but not SBP ($P = 0.412$) (Fig. 5). There was a significant interaction between group and position in HR responses to HUT ($P = 0.044$), but not SBP ($P = 0.065$) or DBP ($P = 0.360$). The change in HR from baseline to 60° HUT was $+26 \pm 8$ beats min^{-1} in COV+ and $+20 \pm 7$ beats min^{-1} in CON ($P = 0.068$). There were no significant main effects of group on SBP ($P = 0.073$), HR ($P = 0.868$) or DBP ($P = 0.253$) during HUT.

Discussion

The purpose of the current study was to investigate autonomic function and haemodynamics in otherwise healthy young adults recently infected with SARS-CoV-2. Our main findings are as follows. Compared with healthy controls, young adults recovering from SARS-CoV-2 (a) exhibit higher resting muscle sympathetic burst frequency, burst incidence and total activity; (b) have higher MSNA burst incidence, but suppressed total MSNA responses during a cold pressor test, and interestingly, rate their pain significantly lower; and (c) display higher MSNA throughout an orthostatic challenge, as well as greater increases in HR. These results suggest that during acute recovery from SARS-CoV-2 infection, autonomic, cardiovascular and perceptual measures at rest and in response to physiological stress may be altered, including both exaggerated (orthostasis) and suppressed (amplitude of MSNA bursts, pain perception) responses compared with healthy young adults. To our knowledge, this is the first study to assess sympathetic neural activity and reactivity following infection with SARS-CoV-2. Given the severity of symptoms and long-term complications that accompany SARS-CoV-2, determining its impact on autonomic function may provide important information for clinicians and scientists in developing targeted treatments and therapies.

Resting sympathetic activity and haemodynamics

In line with our initial hypothesis, young adults recovering from SARS-CoV-2 display elevated resting MSNA, whether expressed as burst frequency, incidence or total activity, compared with age-matched control subjects. These findings are consistent with evidence that increased states of inflammation (e.g. disease), as well as direct infusion of inflammatory cytokines in animal models (Niijima *et al.* 1991; Zhang *et al.* 2003; Helwig *et al.* 2008), are often characterized by marked increases in sympathetic nerve activity (Grassi *et al.* 1995; Dodt *et al.* 2000; Adlan *et al.* 2017; Shorakae *et al.* 2018). While the presence of markers of oxidative stress in other viral diseases is observed, data on SARS-CoV-2 are limited (Choi *et al.* 1996; Liu *et al.* 2017; Menzel *et al.* 2019; Suhail *et al.* 2020). However, animal models have shown elevated concentrations of reactive oxygen species with SARS-CoV infection (van den Brand *et al.* 2014), and human patients exhibit high levels of inflammatory cytokines following infection with each of SARS-CoV and SARS-CoV-2 (Delgado-Roche & Mesta, 2020; Gozalbo-Rovira *et al.* 2020; Ponti *et al.* 2020). Indeed, the oxidative stress and subsequent inflammatory cytokines that accompany SARS-CoV-2 could explain the relatively high resting MSNA observed in our COV+ participants.

Importantly, high levels of MSNA are associated with increased arterial stiffness (Swierblewska *et al.* 2010; Tanaka *et al.* 2017; Holwerda *et al.* 2019). Consistent with this finding, our group recently found a 0.75 m s^{-1} higher carotid-femoral pulse wave velocity (Ratchford *et al.* 2021), as well as increased carotid stiffness and aortic augmentation index (Szeghy *et al.* 2021), in participants recovering from SARS-CoV-2 (many of whom were participants in the current investigation) when compared with healthy controls, indicating increases in arterial

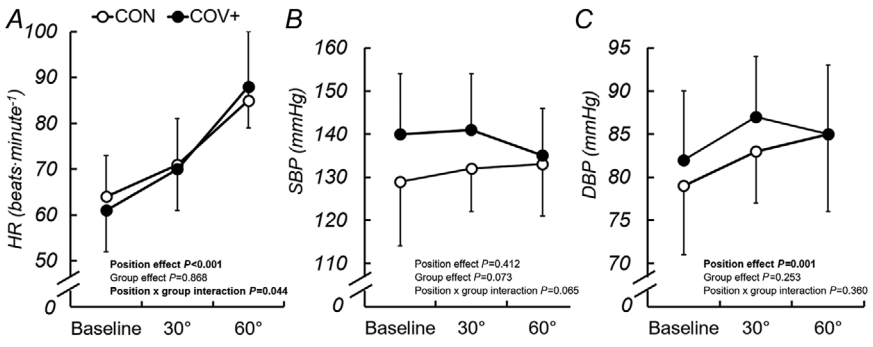

Figure 5. Heart rate (HR) (A), systolic (SBP) (B), and diastolic blood pressure (DBP) (C) before (Baseline) and during 5 min each at 30° and 60° head-up tilt (HUT) in control subjects (CON) and subjects who tested positive for SARS-CoV-2 (COV+)
Two-way repeated measures ANOVA (group-by-body position) were performed between CON (open circles, $n = 14$) and COV+ (closed circles, $n = 16$). Data are mean ± SD.

stiffness in young healthy adults following SARS-CoV-2 infection. Brachial artery flow-mediated dilatation was also significantly blunted in participants recovering from SARS-CoV-2, indicating impaired nitric oxide bioavailability and decreased vascular function (Ratchford *et al.* 2021). Previous work indicates that increased sympathetic outflow may impair the flow-mediated dilatation response (Hijmering *et al.* 2002). Thus, these changes in arterial stiffness and flow-mediated dilatation in young COV+ persons may be due, in part, to the increased sympathetic activity we observed at rest. Notably, the observed changes in MSNA, arterial stiffness and vascular function could be even more of a concern in older persons or those with underlying health conditions following SARS-CoV-2 infection.

Despite higher indices of sympathetic activation following SARS-CoV-2 infection, resting HR, SBP and DBP were not different between COV+ and CON. Further, there were no correlations between measures of MSNA and BP in our participants (all $P \geq 0.730$). These findings are consistent with previous literature wherein young adults (<40 years) exhibit no relationship between MSNA and arterial pressure (Matsukawa *et al.* 1998; Narkiewicz *et al.* 2005; Hart *et al.* 2011), and resting MSNA burst frequency can vary substantially across healthy individuals. Thus, it is not surprising that we might observe differences in MSNA between groups without concomitant differences in blood pressure. However, if a similar elevation in resting MSNA is present in older adults following SARS-CoV-2 infection, there may be more substantial adverse implications for resting haemodynamics (e.g. increased resting blood pressure), as there is a significant positive relationship between MSNA and arterial pressure in both older men and women (Hart *et al.* 2012). Interestingly, patients with COVID-19 have presented with vascular (e.g. pulmonary artery, retinal vessels) enlargement (Caruso *et al.* 2020; Li & Xia, 2020; Asikgarip *et al.* 2021). If, in fact, our COV+ participants also have increased resting vessel diameters, the higher resting MSNA could serve as an acute adaptation to systemic vasodilatation. Certainly, we are limited in these interpretations given the cross-sectional nature and short time frame of this study.

The two groups in our study did not differ in measures of sympathetic transduction to BP at rest. In contrast, the two groups did exhibit differential blood pressure responses to periods of sympathetic quiescence; specifically, individuals recovering from SARS-CoV-2 exhibited smaller drops in MAP in the absence of bursts of MSNA. There are a number of potential mechanisms for this observation, including differences in adrenergic receptor activity (Lurie *et al.* 1985; Mills *et al.* 1990), neurotransmitter release and/or reuptake (Mills *et al.* 1990; Herbison *et al.* 2000), arterial distensibility/elasticity (Nardone *et al.* 2020), hypothalamic–pituitary–adrenal (HPA) axis response (Arlt *et al.* 2003), other systemic vasoconstriction, and non-adrenergic vasoconstrictor mechanisms such as activation of the renin–angiotensin–aldosterone system (RAAS) (Bourgonje *et al.* 2020) or nitric oxide bioavailability (Ratchford *et al.* 2021).

Down regulation/decreased activity of α_2-adrenergic receptors, responsible for neurotransmitter reuptake, could increase noradrenaline binding at α_1-receptors, which in theory may prolong the downstream vascular response (Herbison *et al.* 2000). These changes may explain the increased BP maintenance in the COV+ group to periods of sympathetic quiescence (Coovadia *et al.* 2020). Another possibility is that greater elasticity of blood vessels could increase the ability to maintain blood pressure during sympathetic quiescence (Coovadia *et al.* 2020; Nardone *et al.* 2020). However, our earlier work indicates that, in fact, COV+ participants may present with higher arterial stiffness (and thus less elasticity) and less dilatation in response to shear stress (Ratchford *et al.* 2021), so it is unlikely that differences in blood vessel distensibility explain the differential maintenance of pressure in the absence of MSNA between groups.

Hypothalamic and pituitary tissues also express ACE2, making them a potential target of SARS-COV-2, which could certainly impact the tightly regulated HPA axis and decrease the body's ability to maintain homeostasis during a stress like SARS-CoV-2 Indeed, autopsies of individuals who died from SARS-CoV-2 indicate degeneration of adrenal cortical cells, suggesting altered cortisol dynamics (Pal, 2020). Changes in HPA axis function could potentially impact resting sympathetic activity (Arlt *et al.* 2003), as well as the sustained BP responses in the COV+ group during sympathetic quiescence. The prolific ACE2 receptor is also a key enzyme in the downregulation of the RAAS. SARS-CoV-2 binding to ACE2 and subsequent over-activation of RAAS can result in accumulation of angiotensin 2 and thus vasoconstriction, as well as increased sodium and water reabsorption. While we did not assess any markers of RAAS activation in the current study, it is possible that alterations to RAAS regulation could affect the BP response to sympathetic quiescence (Bourgonje *et al.* 2020; Mourad & Levy, 2020).

Finally, we only measured sympathetic neural activity to the skeletal muscle vasculature, and, while this is generally reflective of total sympathetic activation, it is certainly a possibility that vasoconstriction in renal and/or splanchnic beds could be contributing to the greater maintenance of systemic BP following non-bursts in COV+ participants (Rowell *et al.* 1972; Macefield & Henderson, 2019).

Responses to cold pressor test

The CPT is known to elicit increases in arterial pressure and MSNA, making it ideal for the evaluation of autonomic function (Victor *et al.* 1987; Yamamoto *et al.* 1992; Fu *et al.* 2002; Lamotte *et al.* 2021). In the current study, the COV+ CPT response (i.e. increases in MSNA bursts and BP) was largely intact, with similar haemodynamic responses between groups and higher overall burst incidence in COV+ as compared to CON, consistent with what we observed at rest. Evidence for substantial neurological/psychological dysfunction following SARS-CoV-2 infection is mounting (Li & Xia, 2020; Qin *et al.* 2021; Stefano *et al.* 2021; Taquet *et al.* 2021), and – especially given the elevated basal MSNA measures we observed – we likewise expected that MSNA burst frequency and total activity would be elevated throughout a painful stimulus; however, sympathetic burst frequency and total activity were similar between groups. The CPT, in contrast to resting and orthostatic conditions, allows evaluation of non-baroreflex-mediated sympathetic neural control (Victor *et al.* 1987), though, importantly, baroreceptor function remains intact, but reset, during the CPT (Cui *et al.* 2002). Thus, our findings suggest mild infection with SARS-CoV-2 does not impact the efferent arm of the sympathetic arc.

Previous findings have indicated interindividual variability in the autonomic and cardiovascular responses to the CPT and other painful stimuli (Benetos & Safar, 1991), wherein 'responders' and 'non-responders' exhibit increases and decreases in MSNA and/or BP, respectively. The autonomic and pressure responses tend to move in parallel (Victor *et al.* 1987), though not always (Benetos & Safar, 1991); these divergent groups also show differences in their ratings of pain during the stimulus, with higher perceived pain reported in those exhibiting greater sympathetic outflow and BP responses (Victor *et al.* 1987; Fagius *et al.* 1989; Huang *et al.* 2021; Watso *et al.* 2021). Our findings are consistent with this previously established relationship between pain perception and sympathetic response, as the COV+ participants in the current study had smaller absolute increases in MSNA in the first 30 s of the CPT compared with CON ($+2.9 \pm 8.4$ *vs.* $+9.5 \pm 5.6$ bursts min^{-1}; $+5 \pm 12$ *vs.* $+10 \pm 9$ bursts 100 heart beats^{-1}; $+51 \pm 172$ *vs.* $+243 \pm 36$ a.u. min^{-1}), though this may be a consequence of their higher resting activity, while simultaneously reporting less pain (5.7 ± 1.8 *vs.* 7.1 ± 1.9 a.u.). Pain perception is subjective by nature and can be influenced by the peripheral nervous system via differing nociceptor density and sensitivity, as well as central nervous system modulations. It is unknown whether peripheral and/or central mechanisms are altered by SARS-CoV-2 to result in the relatively low pain perceived by COV+ during the CPT in the current study. However, there is accumulating evidence that coronavirus infections (including SARS-CoV-2) can impact the structure and function of the central nervous system, resulting in prolonged mental and cognitive changes (Qin *et al.* 2021; Stefano *et al.* 2021).

Responses to orthostatic challenge

Consistent with what we observed at rest, MSNA was higher overall in COV+ during the orthostatic challenge compared with CON, though the responses to HUT (i.e. group-by-position interaction and delta MSNA) were largely similar. Due to difficulties with maintaining the microneurographic signal in all participants during tilting, HRV was also used to assess cardiovascular responses to orthostasis. Unexpectedly, the COV+ group displayed higher overall HRV/indices of parasympathetic tone (RMSSD, pNN50 and HFms) when compared with CON. However, compared with CON, COV+ also had more substantial drops in parasympathetic indices (i.e. RMSSD, HF power) as the degree of orthostatic challenge increased; these changes were accompanied by greater increases in HR and concomitant smaller increases in MSNA burst incidence with tilting.

Previous literature suggests an inverse relationship between HRV and inflammation (Williams *et al.* 2019), and hospitalized patients with COVID-19 exhibit decreased indices of HRV (Hasty *et al.* 2021); thus, our finding that measures of HRV were greater in the COV+ cohort was surprising. Our COV+ participants had experienced quite mild symptoms while infected and throughout the early part of their recovery from SARS-CoV-2, and thus it is possible that measures of HRV would not be substantially affected, especially given the limitations to the measurement (Hayano & Yuda, 2019). However, the responsiveness of our HRV measures to HUT were as expected (Carrasco *et al.* 2003; Terkelsen *et al.* 2012), suggesting that these variables were an accurate index of autonomic function during tilting.

The symptoms of SARS-CoV-2 infection and post-acute sequelae of SARS-CoV-2, or 'long COVID,' are wide-ranging, but there is emerging evidence of orthostatic intolerance with tachycardia in a number of patients (Dani *et al.* 2021; Raj *et al.* 2021; Shouman *et al.* 2021), and long-COVID-induced postural tachycardia syndrome has been identified by the American Autonomic Society (Raj *et al.* 2021) as a plausible secondary lingering illness following acute viral recovery from SARS-CoV-2 (Kanjwal *et al.* 2020; Miglis *et al.* 2020; Umapathi *et al.* 2020). COV+ participants in the current study did exhibit greater tachycardia during tilting than CON participants, though the absolute HR values were not particularly abnormal. In a subset of participants, MSNA was also higher in COV+ compared with CON during HUT, but the change in MSNA with increasing orthostatic challenge

was largely similar between groups. Thus, it appears that while overall indices of MSNA are higher both at rest and during stressors, the response to orthostasis is intact following mild SARS-CoV-2 infection. We did observe a blunted MSNA burst incidence response to HUT in COV+ compared with CON; however, this is simply reflective of the greater HR response, which was likely driven by greater vagal withdrawal during orthostasis. Alternatively, rather than being due to central neural mechanisms, differences in the haemodynamic response to orthostatic stress could be due to behavioural changes related to SARS-CoV-2 infection, such as changes in physical activity or food and fluid consumption. Anosmia was the highest rated symptom of our COV+ participants, and olfactory loss has been shown to alter dietary behaviours, including reducing overall consumption (Aschenbrenner *et al.* 2008). Changes in food/fluid consumption could theoretically impact blood volume (hypovolaemia) and the cardiovascular response to orthostasis. Fatigue, another common complaint among the COV+ participants, may also increase the cardiovascular responses to orthostasis (Benarroch, 2012; Tang *et al.* 2020).

Limitations

One limitation to the current investigation is the fact that control participants were tested prior to the COVID-19 pandemic and subsequent 'lockdown', as institutional precautions prevented us from performing human participant research on individuals who had not been infected with SARS-CoV-2 during the time of this study. Evidence suggests modest increases in levels of anxiety and depression among college-age students during the pandemic (Charles *et al.* 2021; Copeland *et al.* 2021). As these mental health conditions can impact cardiovascular parameters (Cohen *et al.* 2015; Holwerda *et al.* 2018), it is possible that differences observed in the present study are a result of the pandemic, rather than infection *per se*. However, data collection began approximately 8 months after the disease was declared a pandemic – a time at which many of our participants had returned to some face-to-face instruction and were living in 'pandemic pods' with their close peers, which may have relieved some stress and sense of isolation.

Certainly, the biggest limitation to the interpretation of these findings is the cross-sectional nature of the study. This is of particular concern when the primary outcome measure (i.e. MSNA) is characterized by high interindividual variability in healthy adults (Keir *et al.* 2020). Since we do not know the resting MSNA of our COV+ participants prior to infection, it is unknown if the differences in resting MSNA observed between groups were truly a result of SARS-CoV-2 infection. Regression equations have previously been developed to predict MSNA from age and/or BMI for a given sex; however, these variables explain only a portion of the variability in MSNA (i.e.1–41% depending on variable and sex) and are particularly poor at explaining the MSNA variability in non-obese men (Keir *et al.* 2020). Further, our groups were largely similar in age and BMI, as well as physical activity levels, ethnicity, education and environmental factors (e.g. all were Caucasian, non-Hispanic students at a mid-sized American university in a small, rural community). Despite the large between-subject standard deviations in MSNA for a given age, we decided to examine the predictions (Matsukawa *et al.* 1998) for our cohort compared with actual values. The predicted MSNA burst frequencies for the CON males and females and COV+ males and females were 22, 12, 22 and 10 bursts min^{-1}, respectively. While these predicted values for males are greater than our actual values in both groups (again, perhaps due to the limited sensitivity of these prediction equations in young, non-obese males), the predicted values for females are on a par with actual female CON participants but much lower than what we observed in our female COV+ participants. Early evidence suggests females are less likely to be hospitalized and die from COVID-19 compared with males (Alkhouli *et al.* 2020), potentially as a result of a greater immune response to viral infection (Scully *et al.* 2020), while females may exhibit worse symptoms of 'long COVID' (Karlsson *et al.* 2020). Whether or not a sex difference exists in the autonomic recovery from SARS-CoV-2 infection is not entirely clear. Longitudinal tracking of healthy young males and females recovering from SARS-CoV-2 infection is undoubtedly warranted to better understand the impact of the virus on sympathetic neural activity.

Conclusion

Autonomic dysfunction represents a major common denominator among many disease states: cardiovascular disease, chronic lung disease, hypertension, diabetes and obesity (Garg *et al.* 2020; Porzionato *et al.* 2020; Sardu *et al.* 2020; Zhou *et al.* 2020). While the involvement of the autonomic nervous system in certain disease states is well-established, its role in the propagation of and recovery from SARS-CoV-2 is complex and relatively unknown. Here, we show for the first time that young and otherwise healthy individuals who have recently been diagnosed with SARS-CoV-2 may have reductions in autonomic function, as supported by higher resting sympathetic activity and cardiovascular responses to orthostasis compared with healthy controls. Additionally, the COV+ group display decreased sensitivity in the BP response to periods of sympathetic quiescence. Further research is necessary to elucidate the underlying mechanisms behind these observed disruptions.

Clinical significance

The potential long-term effects of dysregulated autonomic responses via SARS-CoV-2 should not be overlooked. While our data reflect young and otherwise healthy individuals with no comorbid conditions, these individuals are not representative of those who are most impacted by the virus. If similar autonomic dysregulation is present in older adults following SARS-CoV-2 infection, there may be more substantial adverse implications for cardiovascular health. Future directions should include longitudinal tracking of autonomic function following SARS-CoV-2 in both young and older populations.

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Additional information

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors have no competing interests to declare.

Author contributions

J.L.S, S.M.R. and A.S.L.S. conceived and designed research; N.L.S., V.M.P., M.A.A., J.L.S., S.M.R. and A.S.L.S. performed experiments; N.L.S., J.L.S., S.M.R. and A.S.L.S. analysed data; N.L.S., V.M.P., M.A.A., J.L.S., S.M.R. and A.S.L.S. interpreted results of experiments; N.L.S. and A.S.L.S prepared figures; N.L.S. and A.S.L.S. drafted manuscript; N.L.S., V.M.P., M.A.A., J.L.S., S.M.R. and A.S.L.S. edited and revised manuscript. All authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Keywords

autonomic function, cold pressor test, COVID-19, heart rate variability, MSNA, orthostatic

Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

Statistical Summary Document
Peer Review History