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RESEARCH PAPER

Altered central and peripheral haemodynamics during rhythmic handgrip exercise in young adults with SARS-CoV-2

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Abstract

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can have a profound impact on vascular function. While exercise intolerance may accompany a variety of symptoms associated with SARS-CoV-2 infection, the impact of SARS-CoV-2 on exercising blood flow (BF) remains unclear. Central (photoplethysmography) and peripheral (Doppler ultrasound) haemodynamics were determined at rest and during rhythmic handgrip (HG) exercise at 30% and 45% of maximal voluntary contraction (MVC) in young adults with mild symptoms 25 days after testing positive for SARS-CoV-2 (SARS-CoV-2: n = 8M/5F; age: 21 ± 2 years; height: 176 ± 11 cm; mass: 71 ± 11 kg) and were cross-sectionally compared with control subjects (Control: n = 8M/5F; age: 27 ± 6 years; height: 178 ± 8 cm; mass: 80 ± 25 kg). Systolic blood pressure, end systolic arterial pressure and rate pressure product were higher in the SARS-CoV-2 group during exercise at 45% MVC compared with controls. Brachial artery BF was lower in the SARS-CoV-2 group at both 30% MVC (Control: 384.8 ± 93.3 ml min^{-1}; SARS-CoV-2: 307.8 ± 105.0 ml min^{-1}; P = 0.041) and 45% MVC (Control: 507.4 ± 109.9 ml min^{-1}; SARS-CoV-2: 386.3 ± 132.5 ml min^{-1}; P = 0.002). Brachial artery vascular conductance was lower at both 30% MVC (Control: 3.93 ± 1.07 ml min^{-1} mmHg^{-1}; SARS-CoV-2: 3.11 ± 0.98 ml min^{-1} mmHg^{-1}; P = 0.022) and 45% MVC (Control: 4.74 ± 1.02 ml min^{-1} mmHg^{-1}; SARS-CoV-2: 3.46 ± 1.10 ml min^{-1} mmHg^{-1}; P < 0.001) in the SARS-CoV-2 group compared to control group. The shear-induced dilatation of the brachial artery increased similarly across exercise intensities in the two groups, suggesting the decrease in exercising BF may be due to microvascular impairments. Brachial artery BF is attenuated during HG exercise in young adults recently diagnosed with mild SARS-CoV-2, which may contribute to diminished exercise capacity among those recovering from SARS-CoV-2 like that seen in severe cases.

KEYWORDS
COVID-19, exercising blood flow, nitric oxide, rhythmic handgrip, SARS-CoV-2

1 | INTRODUCTION

The novel coronavirus disease of 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in over 3.9 million fatalities and afflicted nearly 185 million individuals worldwide by June 2021 (World Health Organization, 2021). Critical care, mild and asymptomatic individuals diagnosed with SARS-CoV-2 exhibit a wide range of symptoms, indicating systemic consequences of the virus (Chen et al., 2020; Gallo Marin et al., 2021; Ratchford et al., 2021). The observed decrements in physiological function of those with SARS-CoV-2 may be explained 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) and may be driven by the systemic-inflammatory response, known as the cytokine storm (Channappanavar & Perlman, 2017; Li et al., 2020; Paybast et al., 2020). Indeed, increases in reactive oxygen species observed in animal models with SARS-CoV-2 (van den Brand et al., 2014) and subsequent inflammatory cytokines observed in patients with SARS-CoV-2 (Delgado-Roche & Mesta, 2020; Gozalbo-Rovira et al., 2020; Ponti et al., 2020) could negatively impact multiple organ systems (Ferm et al., 2020; Jothimani et al., 2020; Siripanthong et al., 2020), including the vasculature (Poole et al., 2021; Wadley et al., 2013). This impact on the vasculature may lead to significant functional decreases when physiological systems are stressed such as during activities of daily living or exercise.

Several investigations have reported decreases in vascular regulation at rest (Paneroni et al., 2021; Ratchford et al., 2021; Riou et al., 2021), as well as increases in arterial stiffness (Jud et al., 2021; Szeghy et al., 2022) long after SARS-CoV-2 infection, which may have consequences for oxygen and substrate transport to and from active tissues such as skeletal muscle during exercise. While deficits in exercise capacity have been observed 6 (Hui et al., 2005) and 14 (Su et al., 2007) months after diagnosis of severe acute respiratory syndrome (SARS), recent accounts of exercise intolerance among those recovering from SARS-CoV-2 have only begun to emerge. Lower peak oxygen consumption and ventilatory efficiency during cardiopulmonary exercise testing (Raman et al., 2021) and shorter 6-min walk distance (Huang et al., 2021) among individuals who have been hospitalized with SARS-CoV-2 may ultimately be related to vascular dysregulation following SARS-CoV-2 infection.

Therefore, the purpose of this investigation was to assess the potential impact of SARS-CoV-2 on central and peripheral haemodynamics during rhythmic isometric handgrip (HG) exercise. To address this aim, we examined the central and peripheral haemodynamics during rhythmic HG exercise in young adults recovering from SARS-CoV-2. We compared young adults who had recently tested positive for SARS-CoV-2 with otherwise healthy young adults whose data were collected prior to the COVID-19 pandemic. We used a small-muscle mass HG exercise to minimize central haemodynamic perturbation during exercise, and we hypothesized central haemodynamics would be similar between the SARS-CoV-2 and the control groups in response to exercise. However, we further hypothesized that peripheral haemodynamics, as evidenced by a lower exercise hyperaemic response to HG, would be blunted in the SARS-CoV-2 group compared to the healthy control group. These data would, therefore, provide insight into the role of peripheral blood flow (BF) regulation during exercise among adults who recently tested positive for SARS-CoV-2 and may shed light on the potential mechanisms for exercise intolerance in patients hospitalized following infection.

New Findings

- **What is the central question of this study?**
  Are central and peripheral haemodynamics during handgrip exercise different in young adults 3–4 weeks following infection with of SARS-CoV-2 compared with young healthy adults.
- **What is the main finding and its importance?**
  Exercising heart rate was higher while brachial artery blood flow and vascular conductance were lower in the SARS-CoV-2 compared with the control group. These findings provide evidence for peripheral impairments to exercise among adults with SARS-CoV-2, which may contribute to exercise limitations.

2 | METHODS

2.1 | Ethical approval

All procedures were approved by the Appalachian State University Institutional Review Board (IRB_20-0304, IRB_20-0132) as well as the University of Utah and Salt Lake City VA Medical Center Institutional Review Boards (IRB_00030810). The study conformed to the standards set by the *Declaration of Helsinki*, except for registration in a database. Prior to testing, experimental procedures were explained to participants, both in writing and verbally, and subjects provided written informed consent.

2.2 | Subjects

Young adults who tested positive for SARS-CoV-2 using a nasopharyngeal swab polymerase chain reaction assay in the prior 3–4 weeks reported to the laboratory. Control data were previously collected at Appalachian State University (Boone, NC, USA) and University of Utah (Salt Lake City, UT, USA) and were collected prior to the first confirmed case of COVID-19 in North Carolina, USA (3

March 2020) or in Salt Lake City, UT (6 March 2020). Control subjects were selected based on similar age, sex, height, mass, body mass index (BMI) and maximum voluntary contraction. Control subjects did not report any flu-like symptoms. All subjects were non-smokers, free from cardiovascular, metabolic, or renal disease, and female participants were not currently pregnant or breastfeeding. SARS-CoV-2 subjects did not require hospitalization during or following infection.

2.3 | Study procedures

For testing, participants arrived at the laboratory having abstained from exercise, caffeine and alcohol for at least 24 h before testing, and ≥4 h postprandial. Anthropometric data were collected upon arrival to the laboratory to calculate body surface area (BSA) using the Haycock method as: BSA (m^2) = 0.024265 × (height, m)$^{0.3964}$ × (weight, kg)$^{0.5378}$. Participants lay supine on a bed for instrumentation. Testing took place in a quiet, environmentally controlled laboratory, with an ambient temperature of ~23°C in a lightly dimmed room.

2.4 | SARS-CoV-2 symptom severity survey

Subjects who tested positive for SARS-CoV-2 were asked to rank their SARS-CoV-2 symptoms on the day of study testing. On a scale of 0–100 of increasing severity, subjects ranked their symptoms of 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, difficulty breathing, dyspnoea, sore joints or sore throat. The values for all symptoms were totalled and averaged for total symptom severity. Mild symptoms were categorized as a symptom severity score of 0–33, moderate as 34–66 and severe as 67–100.

2.5 | Rhythmic handgrip exercise

Subjects were in the supine position for ~20 min before the start of data collection with the right arm abducted 90° and the elbow joint extended at heart level. Resting measurements were obtained for 1 min prior to HG exercise. Maximal voluntary contraction (MVC) was established by taking the highest value of three maximal contractions using an isometric HG dynamometer (TSD121C, Biopac Systems, Goleta, CA, USA). Rhythmic HG exercise was performed at 30% (moderate intensity) and 45% (high intensity) MVC for 3 min each with 2 min rest between workloads. Force output was continuously displayed for visual feedback to ensure subjects reached the desired rapid force production during each isometric contraction (AcqKnowledge Data Acquisition, Biopac Systems). Rapid contractions were performed at 1 Hz frequency while using a metronome for auditory feedback. Central and peripheral haemodynamic measurements were obtained during the last 60 s of each stage. Rating of perceived exertion on a 10-point scale (RPE/10: 1–10, with 10 being maximal effort) was indicated by the subject during the last 30 s of each exercise stage.

2.6 | Central haemodynamic variables

Heart rate (HR), stroke volume (SV) and cardiac output (CO) were determined using beat-by-beat photoplethysmography (NOVA, Finapres Medical Systems, Enschede, The Netherlands). HR was monitored from a standard three-lead electrocardiogram recorded on the data acquisition system (Biopac). SV was calculated using the Modelflow method, which includes age, sex, height and weight (Beatscope version 1.1; Finapres Medical Systems) (Bogert & van Lieshout, 2005) and has been documented to accurately track SV during a variety of experimental protocols, including exercise (de Vaal et al., 2005; de Wilde et al., 2009; Sugawara et al., 2003). CO was calculated as: CO (l min^{-1}) = HR × SV. Stroke index (SI; ml m^{-2}) and cardiac index (CI; l min^{-1} m^{-2}) were calculated relative to BSA (m^2). Pulse pressure (PP), a measure of pulsatile arterial afterload, the non-resistive oscillatory component of arterial afterload (Chemla et al., 1998; Kelly et al., 1992), was calculated as: PP (mmHg) = systolic arterial pressure (SAP) − diastolic arterial pressure (DAP). MAP was calculated as: MAP (mmHg) = DAP + (PP × 0.33). Rate pressure product (RPP), an indication of myocardial oxygen consumption (Kitamura et al., 1972), was calculated as: RPP (A.U.) = SAP × HR. End systolic arterial pressure (P_{es}) was calculated as (Kelly et al., 1992): P_{es} (mmHg) = 0.9 × SAP. Effective arterial elastance (E_a), an index of total arterial afterload (Kelly et al., 1992), was calculated as: E_a (mmHg ml^{-1}) = P_{es} × SV^{-1}. Stroke work (SW), known as a measure of left systolic work (Kelly et al., 1992), was calculated as: SW (mmHg ml) = P_{es} × SV. Total arterial compliance (TAC), an index of pulsatile arterial afterload while considering the effect of SV (Chemla et al., 1998; Reil et al., 2013), was calculated as: TAC (ml $mmHg^{-1}$) = SV × PP^{-1}.

2.7 | Peripheral haemodynamic variables

Baseline measurements of the right brachial artery diameter and blood velocity were taken for 1 min using a Doppler ultrasound system (GE Logiq eR7 and L4-12T-RS transducer, GE Medical Systems, Milwaukee, WI, USA). Sample volume was optimized in relation to vessel diameter and centred within the vessel for each subject. Measurements of brachial artery diameter and velocity were obtained with the Doppler ultrasound in duplex mode with B-mode imaging frequency of 12 MHz and Doppler frequency of 4 MHz. An angle of insonation of 60° was achieved for all measurements (Rizzo et al., 1990). Brachial artery mean diameters were analysed offline as second-averages to calculate mean forearm blood flow (FBF). Anterograde and retrograde brachial artery diameters were obtained from diameter measurements made at 30 Hz and determined as maximum and minimum diameters, respectively, every second to calculate anterograde FBF (aFBF)

TABLE 1 Subject characteristics

	Control (8 M/5 F)	SARS-CoV-2 (8 M/5 F)	*P*
Age (years)	27.4 ± 6.3	21.3 ± 1.9[a]	0.003
Height (cm)	178 ± 8	176 ± 11	0.614
Body mass (kg)	80 ± 25	71 ± 11	0.244
Body mass index (kg m^{-2})	25.2 ± 6.6	23.1 ± 2.3	0.321
Handgrip MVC (kg)	27.7 ± 5.8	28.2 ± 7.6	0.850
Handgrip 30% MVC (kg)	8.3 ± 1.7	8.4 ± 2.3	0.845
Handgrip 45% MVC (kg)	12.4 ± 2.6	12.7 ± 3.4	0.845
SSRI use (*n*)	2 F	3 F	

Data are means ± SD. Two-tailed Student's *t* tests were used to compare groups.
[a]$P < 0.05$ between groups. Abbreviations: MVC, maximal voluntary contraction; SSRI, Selective Serotonin Reuptake Inhibitor.

and retrograde FBF (rFBF), respectively (Cardiovascular Suite v. 4.0, Quipu, Pisa, Italy). Ultrasound Doppler measurements of mean blood velocity (V_{mean}), anterograde blood velocity (V_{antro}), and retrograde blood velocity (V_{retro}) were derived as the intensity-weighted mean, above baseline, and below baseline, respectively, blood velocity on the GE Doppler ultrasound during the last 60 s of each exercise intensity for the determination of limb BF at steady state exercise. The FBF was calculated as: FBF (ml min^{-1}) = [V_{mean} × π (mean vessel diameter × $2^{-1})^2$ × 60]. The aFBF was calculated as: aFBF (ml min^{-1}) = [V_{antro} × π (anterograde vessel diameter × $2^{-1})^2$ × 60]. The rFBF was calculated as: rBF (ml min^{-1}) = [V_{retro} × π (retrograde vessel diameter × $2^{-1})^2$ × 60]. Forearm vascular conductance (FVC) was calculated as: FVC (ml min^{-1} $mmHg^{-1}$) = FBF × MAP^{-1}. Anterograde forearm vascular conductance (aFVC) was calculated as: aFVC (ml min^{-1} $mmHg^{-1}$) = aFBF × SAP^{-1}. Retrograde forearm vascular conductance (rFVC) was calculated as: rFVC (ml min^{-1} $mmHg^{-1}$) = rFBF × DAP^{-1}. Shear rate (SR) was calculated as: SR (s^{-1}) = 8 × V_{mean} × arterial $diameter^{-1}$. Anterograde shear rate (aSR) was calculated as: aSR (s^{-1}) = 8 × V_{antro} × anterograde vessel $diameter^{-1}$. Retrograde shear rate (rSR) was calculated as: rSR (s^{-1}) = 8 × V_{retro} × retrograde vessel $diameter^{-1}$.

2.8 | Statistical analyses

Statistics were performed using commercially available software (SigmaStat 14.0; Systat Software, Point Richmond, CA, USA). Subject characteristics were compared using a two-tailed Student's *t*-test for two samples of equal variance. A 2 × 3 repeated-measures ANOVA ($P < 0.05$) (group, 2 levels: Control vs. SARS-CoV-2) (workload, 3 levels: rest, 30 and 45% of MVC) was performed to compare the haemodynamic responses in control and SARS-CoV-2 groups during exercise with pairwise comparisons when a significant interaction was found. The Brown–Forsythe method was used to assess equality of variances and the Shapiro–Wilk test to assess normality of data. The Bonferroni *t*-test method was used for α adjustment and *post hoc* analysis for multiple comparisons. The slope of the shear rate over brachial artery diameter was compared between groups using a two-tailed Student's *t*-test. Data are expressed as means ± SD.

3 | RESULTS

3.1 | Subject characteristics

Subject characteristics are presented in Table 1. While the control group was significantly older than the SARS-CoV-2 group, the height, body mass, BMI and HG MVC among these groups were not different. The RPE/10 at 30% MVC (Control: 5.5 ± 1.9 AU, SARS-CoV-2: 4.3 ± 2.1 AU, $P = 0.20$) and 45% MVC (Control: 7.5 ± 1.6 AU, SARS-CoV-2: 7.3 ± 1.9 AU, $P = 0.33$) were similar between groups. Two females in control and all five females in the SARS-CoV-2 group were taking prescribed contraception, and all were pre-menopausal. Two and three female subjects from the control and SARS-CoV-2 groups, respectively, were prescribed selective serotonin reuptake inhibitors.

3.2 | SARS-CoV-2 symptom severity survey

SARS-CoV-2 subjects rated their symptoms on the day of study testing on a scale of 0–100, with symptom averages among those subjects experiencing symptoms being displayed in parentheses. One subject reported mild chest pain (30 AU), two reported symptoms of mild dizziness/vertigo (15 ± 7 AU), two reported lack of appetite (25 ± 21 AU), three reported having a mild dry cough (18 ± 19 AU), three reported moderate anosmia (38 ± 25 AU), three reported mild muscle or body aches (7 ± 3 AU), three reported mild dyspnoea (12 ± 8 AU), and three reported mild sore throats (9 ± 7 AU), four reported mild dry eyes (11 ± 6 AU), five reported mild dry mouth (11 ± 2 AU), seven reported mild fatigue (19 ± 11 A.U.) and seven reported nasal congestion (11 ± 9 AU). No subjects reported symptoms of chills, diarrhoea, fever, headache, nausea or sore joints. Collectively, subjects averaged 3.4 ± 2.1 symptoms with a severity of 15.1 ± 6.8 AU which was classified as mild symptoms on the day of testing.

TABLE 2 Central haemodynamic responses to rhythmic handgrip exercise

					P		
		Baseline	30% MVC	45% MVC	Group	Workload	Interaction effect
Systolic blood pressure (mmHg)	Control	124 ± 5	132 ± 5[a]	142 ± 6[a,b]	0.243	<0.001	0.043
	SARS-CoV-2	123 ± 10	137 ± 14[a]	151 ± 19[a,b,c]			
Diastolic blood pressure (mmHg)	Control	75 ± 7	82 ± 8	90 ± 11	0.896	<0.001	0.321
	SARS-CoV-2	72 ± 7	81 ± 11[a]	93 ± 14			
Pulse pressure (mmHg)	Control	48 ± 6	50 ± 7	51 ± 7	0.050	<0.001	0.055
	SARS-CoV-2	51 ± 6	56 ± 6	59 ± 8			
Stroke index (ml m^{-2})	Control	43 ± 7	43 ± 7	41 ± 7	0.050	<0.001	0.720
	SARS-CoV-2	46 ± 10	47 ± 11	43 ± 13			
Stroke work (mmHg l^{-1})	Control	9.46 ± 2.15	10.11 ± 2.60	10.49 ± 2.97[a]	0.757	<0.001	0.686
	SARS-CoV-2	9.55 ± 2.80	10.62 ± 3.04	10.92 ± 3.6			
Cardiac index (l min^{-1} m^{-2})	Control	2.34 ± 0.47	2.71 ± 0.94	2.84 ± 0.77[a]	0.036	<0.001	0.328
	SARS-CoV-2	2.81 ± 0.65	3.41 ± 0.89[a]	3.73 ± 1.35[a,c]			
End systolic arterial pressure (mmHg)	Control	112 ± 4	119 ± 5[a]	127 ± 5[a,b]	0.243	<0.001	0.043
	SARS-CoV-2	111 ± 9	123 ± 13[a]	136 ± 17[a,b,c]			
Total arterial compliance (ml $mmHg^{-1}$)	Control	1.78 ± 0.49	1.72 ± 0.54	1.62 ± 0.48[a]	0.378	<0.001	0.097
	SARS-CoV-2	1.69 ± 0.43	1.56 ± 0.41[a]	1.38 ± 0.46[a,b]			
Systemic vascular conductance (ml min^{-1} $mmHg^{-1}$)	Control	5.11 ± 1.49	5.28 ± 1.88	5.34 ± 2.05	0.195	0.194	0.510
	SARS-CoV-2	5.89 ± 1.62	6.40 ± 1.73	6.19 ± 2.11			
Effective arterial elastance (mmHg ml^{-1})	Control	1.39 ± 0.35	1.49 ± 0.38	1.65 ± 0.39[a]	0.594	<0.001	0.096
	SARS-CoV-2	1.38 ± 0.39	1.53 ± 0.47	1.90 ± 0.77[a,b]			
Rate pressure product (mmHg bpm)	Control	6826 ± 1128	7965 ± 1592	9,727 ± 1,928[a,b]	0.001	<0.001	0.003
	SARS-CoV-2	7608 ± 1198	10,084 ± 1497[a,c]	12,975 ± 2686[a,b,c]			

Data are means ± SD. A 2 × 3 repeated measures ANOVA ($\alpha < 0.05$) (group, 2 levels; Control vs. SARS-CoV-2; workload, 3 levels: baseline, 30%, and 45% MVC) was performed to compare shear and brachial artery responses in control and SARS-CoV-2 groups.

[a] $P < 0.05$ versus baseline groups pooled.

[b] $P < 0.05$ versus 30% MVC within group.

[c] $P < 0.05$ between groups within condition.

3.3 | Central haemodynamics

The central haemodynamic responses to the rhythmic HG exercise are detailed in Table 2. Interaction effects (group × workload) were observed for SBP, P_{es} and RPP, with the measures of the SARS-CoV-2 group being elevated when compared with the measures of the control group during incremental exercise (Table 2). There was a main effect of group for CI, PP and SI with the measures in the SARS-CoV-2 group being elevated when compared with the control measures. A main effect for group was observed for HR ($P = 0.007$) with the SARS-CoV-2 group being elevated (Figure 1). There were no interaction effects or main effects of group for DBP, MAP, SV, CO, SW, TAC or E_a (Table 2).

3.4 | Peripheral haemodynamics

Brachial artery diameter progressively increased in both groups from baseline to 30% MVC and 45% MVC (see Figure 3b), but there were no differences between groups or group by workload interactions in mean, anterograde, or retrograde brachial artery diameters (Table 3). There was a main effect of intensity for anterograde brachial artery diameter ($P < 0.001$). Retrograde brachial artery diameter did not have an interaction effect or main effect of group, but displayed a main effect of intensity ($P < 0.001$) (Table 3).

There was a group by workload interaction for mean brachial artery FBF ($P = 0.007$) and aFBF ($P = 0.042$), but not rFBF ($P = 0.357$). Mean brachial artery FBF was not different between groups at baseline (Control: 70.9 ± 39.4; SARS-CoV-2: 65.4 ± 33.4 ml min^{-1}; $P = 0.880$) but was different between groups at both 30% MVC (Control: 384.8 ± 93.3; SARS-CoV-2: 307.8 ± 105.0 ml min^{-1}; $P = 0.041$) and 45% MVC (Control: 507.4 ± 109.9; SARS-CoV-2: 386.3 ± 132.5 ml min^{-1}; $P = 0.002$) (Figure 2). The aFBF increased significantly from BL to 30% and 45% MVC in both groups. The aFBF was not different between groups at either baseline (Control: 79.1 ± 43.5; SARS-CoV-2: 71.6 ± 41.1 ml min^{-1}; $P = 0.875$) or 30% MVC (Control: 450.5 ± 144.2; SARS-CoV-2: 387.0 ± 117.0 ml min^{-1}; $P = 0.183$), but was significantly lower in the SARS-CoV-2 group at 45% MVC when compared with

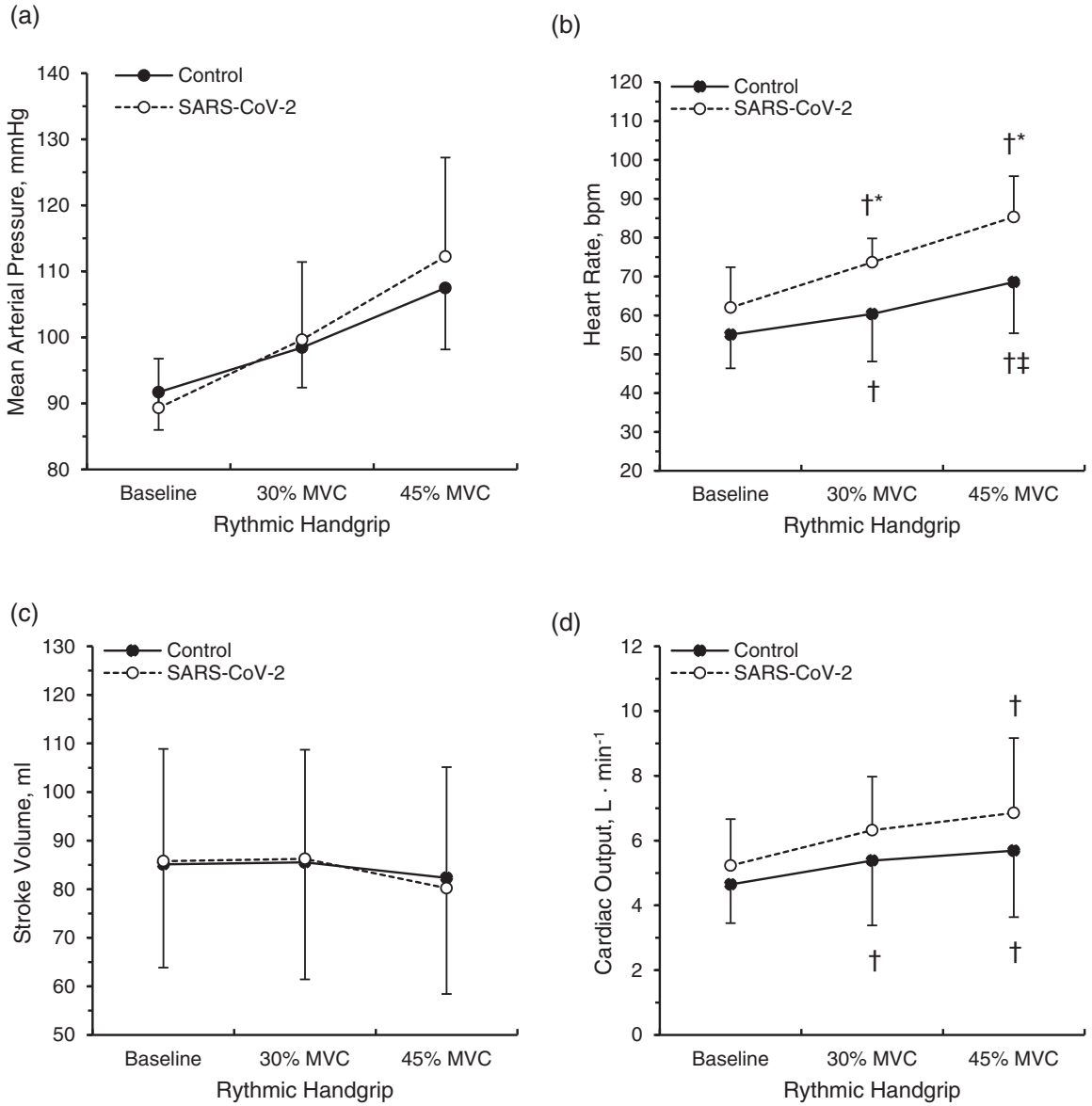

FIGURE 1 Mean arterial pressure (a), heart rate (b), stroke volume (c), and cardiac output (d) responses during supine rhythmic HG in young adults with SARS-CoV-2 and healthy controls. A 2 × 3 repeated measures ANOVA ($\alpha < 0.05$) (group, 2 levels; Control vs. SARS-CoV-2; workload, 3 levels: baseline, 30% and 45% MVC) was performed to compare central haemodynamic responses in control and SARS-CoV-2 groups during exercise with planned comparisons set for workload comparisons to rest. There was a main effect for group for HR ($P = 0.007$) with the SARS-CoV-2 group being elevated compared to healthy controls, but not for MAP ($P = 0.711$), SV ($P = 0.979$) and CO ($P = 0.180$). Data are means ± SD. $^{\dagger}P < 0.05$ versus baseline within group; $^{\ddagger}P < 0.05$ versus 30% MVC within group; $^{*}P < 0.05$ between groups within condition

controls (Control: 615.3 ± 134.4; SARS-CoV-2: 486.0 ± 175.0 ml min^{-1}; $P = 0.009$). There was not a main effect of group ($P = 0.400$) for rFBF, but there was a main effect of intensity ($P < 0.001$).

There were significant group by workload interactions for both mean SR ($P = 0.011$) and aSR ($P = 0.017$). The mean SR was similar between groups at baseline (Control: 184 ± 99 s^{-1} *vs.* SARS-CoV-2: 154 ± 43 s^{-1}; $P = 0.625$) and 30% MVC (Control: 796 ± 235 s^{-1} *vs.* SARS-CoV-2: 676 ± 153 s^{-1}; $P = 0.056$) but significantly lower at 45% MVC in the SARS-CoV-2 group (727 ± 135 s^{-1}) compared with the controls (925 ± 194 s^{-1}) ($P = 0.002$) (Figure 3a). The aSR was not different between groups at baseline ($P = 0.594$) or 30% MVC ($P = 0.159$) but was different between groups at 45% MVC ($P = 0.003$) (Table 3). There was not a significant interaction effect ($P = 0.075$) or main effect for group ($P = 0.226$) for rSR, but there was a main effect for intensity for rSR ($P < 0.001$).

There was an interaction effect for mean FVC ($P = 0.002$) and aFVC ($P = 0.011$). The mean FVC was lower in the SARS-CoV-2 group at 30% ($P = 0.022$) and 45% MVC ($P < 0.001$) (Table 3). The aFVC was lower at 45% MVC in the SARS-CoV-2 group when compared with the control group ($P = 0.002$) (Table 3). There was not an interaction effect ($P = 0.301$) or main effect for group ($P = 0.438$) for rFVC, but there was a main effect for intensity for rFVC ($P < 0.001$).

TABLE 3 Peripheral haemodynamic responses to rhythmic handgrip exercise

					P		
		Baseline	30% MVC	45% MVC	Group	Workload	Interaction effect
Anterograde brachial artery diameter (cm)	Control	0.42 ± 0.05	0.45 ± 0.05[a]	0.47 ± 0.05[a]	0.702	<0.001	0.304
	SARS-CoV-2	0.41 ± 0.06	0.44 ± 0.06[a]	0.46 ± 0.07[a,‡]			
Retrograde brachial artery diameter (cm)	Control	0.41 ± 0.05	0.43 ± 0.06[a]	0.44 ± 0.05[a]	0.809	<0.001	0.810
	SARS-CoV-2	0.40 ± 0.06	0.43 ± 0.06[a]	0.43 ± 0.06[a]			
Mean brachial artery diameter (cm)	Control	0.41 ± 0.05	0.44 ± 0.05	0.46 ± 0.05	0.796	<0.001	0.087
	SARS-CoV-2	0.41 ± 0.06	0.43 ± 0.07	0.45 ± 0.07			
Anterograde blood velocity (cm s^{-1})	Control	9.78 ± 4.75	49.96 ± 9.42[a]	59.39 ± 7.14[a,‡]	0.005	<0.001	0.011
	SARS-CoV-2	8.39 ± 2.68	41.72 ± 5.49[a,c]	48.01 ± 5.77[a,‡,c]			
Retrograde blood velocity (cm s^{-1})	Control	−0.66 ± 1.06	−4.45 ± 3.04[a]	−7.69 ± 2.98[a,‡]	0.288	<0.001	0.128
	SARS-CoV-2	−0.55 ± 0.78	−6.60 ± 2.56[a,c]	−8.18 ± 3.75[a]			
Mean blood velocity (cm s^{-1})	Control	9.13 ± 4.54	42.51 ± 7.89[a]	51.70 ± 6.08[a,‡]	<0.001	<0.001	<0.001
	SARS-CoV-2	7.84 ± 2.31	35.12 ± 5.26[a,c]	39.82 ± 4.73[a,‡,c]			
Anterograde shear rate (s^{-1})	Control	194 ± 101	851 ± 225[a]	1,029 ± 186[a,‡]	0.058	<0.001	0.017
	SARS-CoV-2	163 ± 45	771 ± 126[a]	852 ± 103[a,c]			
Retrograde shear rate (s^{-1})	Control	−12 ± 19	−82 ± 50[a]	−140 ± 51[a,‡]	0.226	<0.001	0.075
	SARS-CoV-2	−10 ± 13	−122 ± 38[a,c]	−148 ± 58[a]			
Anterograde vascular conductance (ml min^{-1} $mmHg^{-1}$)	Control	0.65 ± 0.38	3.44 ± 1.24[a]	4.35 ± 0.98[a,‡]	0.041	<0.001	0.011
	SARS-CoV-2	0.58 ± 0.32	2.83 ± 0.79[a]	3.22 ± 1.06[a,c]			
Retrograde vascular conductance (ml min^{-1} $mmHg^{-1}$)	Control	−0.08 ± 0.13	−0.52 ± 0.48[a]	−0.81 ± 0.45[a,‡]	0.438	<0.001	0.301
	SARS-CoV-2	−0.07 ± 0.11	−0.76 ± 0.42[a]	−0.86 ± 0.49[a]			
Mean vascular conductance (ml min^{-1} $mmHg^{-1}$)	Control	0.79 ± 0.48	3.93 ± 1.07[a]	4.74 ± 1.02[a,‡]	0.021	<0.001	0.002
	SARS-CoV-2	0.73 ± 0.30	3.11 ± 0.98[a,c]	3.46 ± 1.10[a,c]			

Data are means ± SD. A 2 × 3 repeated measures ANOVA ($\alpha < 0.05$) (group, 2 levels; Control vs. SARS-CoV-2; workload, 3 levels: baseline, 30%, and 45% MVC) was performed to compare shear and brachial artery responses in control and SARS-CoV-2 groups during exercise with planned comparisons set for workload comparisons to rest.

[a] $P < 0.05$ versus baseline within group.

[‡] $P < 0.05$ versus 30% MVC within group. [c] $P < 0.05$ between groups within condition

When the relationship between SR and the mean brachial artery diameter from rest to 30% MVC and 45% MVC was assessed, similar slopes were observed between the control ($(5.01 \pm 2.76) \times 10^{-5}$ AU cm^{-1}) and the SARS-CoV-2 group ($(5.90 \pm 3.02) \times 10^{-5}$ AU cm^{-1}) ($P = 0.438$) (Figure 3c). Further, when the relationship between SR and the percentage change in mean brachial artery diameter was assessed from 30% MVC to 45% MVC, similar slopes were observed between the control group ($8.78 \times 10^{-2} \pm 1.99 \times 10^{-1}$) and the SARS-CoV-2 group (-1.84 ± 4.86) ($P = 0.429$).

4 | DISCUSSION

The purpose of this study was to investigate the potential differences in central and peripheral haemodynamics during rhythmic HG exercise among those recently diagnosed with SARS-CoV-2 when cross-sectionally compared with young healthy adults. Our hypotheses were partially correct, as young adults with SARS-CoV-2 exhibited many similar central haemodynamic responses to exercise to young healthy adults, but displayed higher SBP, P_{es}, and RPP responses to HG exercise compared with healthy controls. These data suggest several exaggerated central responses to HG exercise among adults with SARS-CoV-2. In line with our second hypothesis, we identified lower brachial artery BF during rhythmic HG exercise at both 30% and 45% MVC in individuals with SARS-CoV-2 compared with healthy control subjects, which appears to be largely driven by differences in anterograde BF response. These data provide additional information as to the oscillatory BF patterns of young adults recovering from SARS-CoV-2, suggesting a potential role for decreased exercising BF contributing to exercise intolerance among those recovering from more severe SARS-CoV-2 infection. Finally, when examining the shear-induced brachial artery vasodilatation, both groups had similar brachial artery diameter responses to two sustained shear stimuli at 30% and 45% MVC, suggesting the impairment in exercising BF may be due to microvascular impairments downstream of the conduit vessel. Taken together, these findings demonstrate an impaired hyperaemic response, but a preservation of conduit vessel endothelial function during small muscle mass exercise in young adults recovering from SARS-CoV-2.

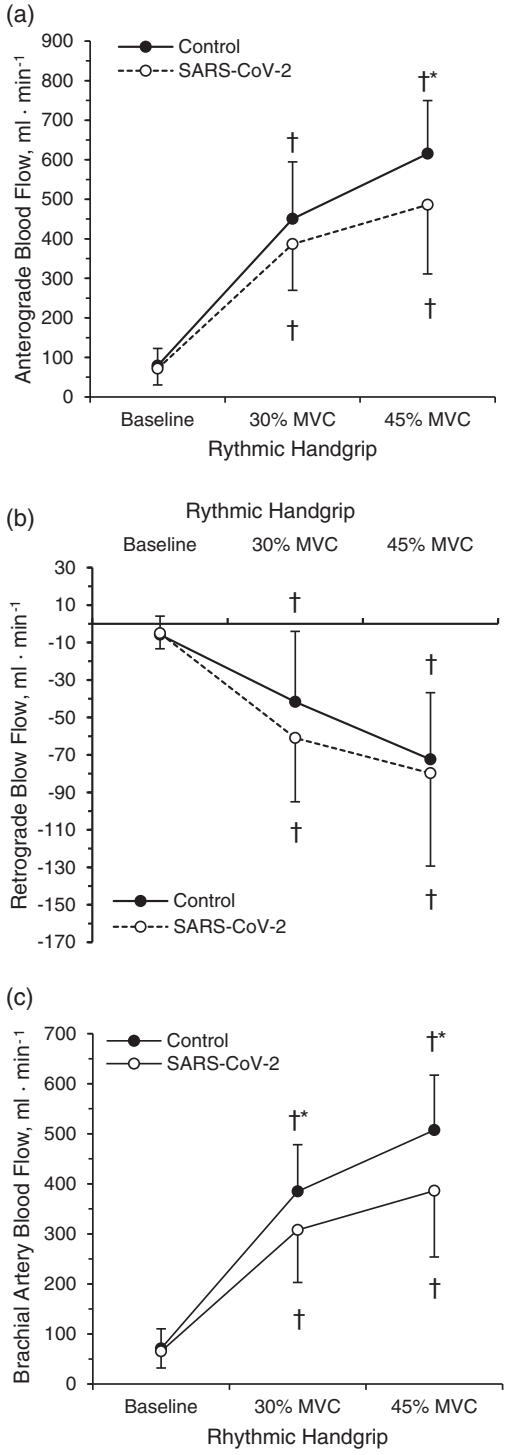

FIGURE 2 Brachial artery anterograde blood flow (a), retrograde blood flow (b), and mean blood flow (c) responses during supine rhythmic HG in young adults with SARS-CoV-2 and healthy controls. A 2 × 3 repeated measures ANOVA ($\alpha < 0.05$) (group, 2 levels; Control vs. SARS-CoV-2; workload, 3 levels: baseline, 30% and 45% MVC) was performed to compare peripheral haemodynamic responses in control and SARS-CoV-2 groups during exercise with planned comparisons set for workload comparisons to rest. There was a main effect for group for mean FBF ($P = 0.007$) with the SARS-CoV-2 group being lower than healthy controls, but not for aFBF ($P = 0.096$) or rFBF ($P = 0.400$). Data are means ± SD. †$P < 0.05$ versus baseline within group; ‡$P < 0.05$ versus 30% MVC within group; *$P < 0.05$ between groups within condition

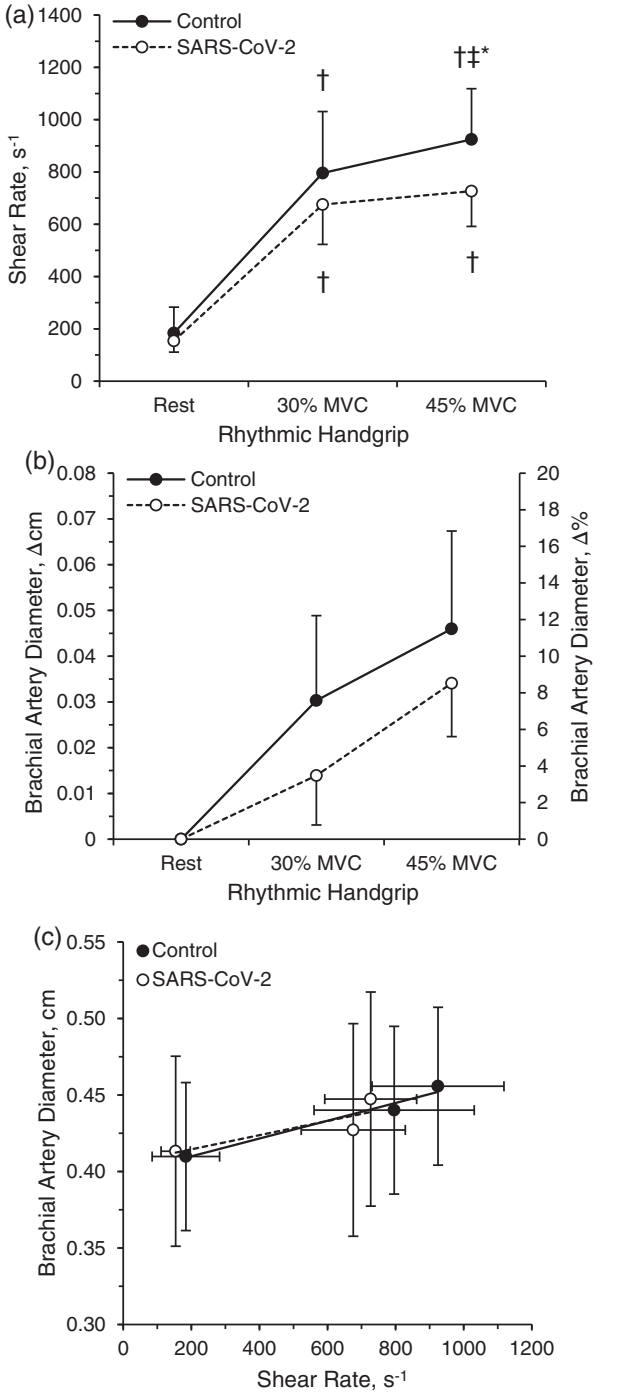

FIGURE 3 Shear rate (a), change in brachial artery diameter (b), and brachial artery diameter as a function of shear rate (c) responses during supine rhythmic HG in young adults with SARS-CoV-2 and healthy controls. A 2 × 3 repeated measures ANOVA ($\alpha < 0.05$) (group, 2 levels; Control vs. SARS-CoV-2; workload, 3 levels: baseline, 30% and 45% MVC) was performed to compare shear and brachial artery responses in control and SARS-CoV-2 groups during exercise with planned comparisons set for workload comparisons to rest. There was a main effect for group for mean shear rate ($P = 0.038$) with the SARS-CoV-2 group being lower than the healthy control group. The slope of the shear rate over brachial artery diameter (c) was compared between groups using a two-tailed Student's *t*-test. Data are means ± SD. †$P < 0.05$ versus baseline within group; ‡$P < 0.05$ versus 30% MVC within group; *$P < 0.05$ between groups within condition

4.1 | Exercising central haemodynamics in SARS-CoV-2

Shortness of breath, lethargy and fatigue are common symptoms of SARS-CoV-2 infection, with cardiac, pulmonary, autonomic, metabolic and vascular factors all likely contributing to the multifactorial nature of the disease. Several investigations have documented impairments in exercise capacity among those recovering from SARS that may last for years (Hui et al., 2005; Ngai et al., 2010; Su et al., 2007), and evidence on exercise limitations following SARS-CoV-2 is rapidly emerging (Huang et al., 2021; Raman et al., 2021). Several investigations have recently observed changes to cardiac structure and function in response to SARS-CoV-2 infection (Babapoor-Farrokhran et al., 2020; Bleakley et al., 2021; Capotosto et al., 2020), highlighting the potential central limitations to exercise capacity among those recovering from SARS-CoV-2. Further, upon hospital discharge, patients recovering from SARS-CoV-2 display significant decreases in exercise capacity (Baratto *et al*., 2021). Interestingly, this group also observed adults recovering from SARS-CoV-2 displayed enhanced chemoreflex sensitivity, as evidenced by augmented hyperventilation during exercise (Baratto *et al*., 2021). Likewise, early observations of exaggerated orthostatic tachycardia among adults with SARS-CoV-2 (Blitshteyn & Whitelaw, 2021; Shouman et al., 2021) highlight the potential role of autonomic dysregulation in the central haemodynamic characteristics associated with SARS-CoV-2. Indeed, in the current investigation, despite matching groups for MVC and consequently observing several similar central haemodynamic responses to exercise, we observed a higher HR during small muscle mass exercise in adults with SARS-CoV-2 compared with healthy adults (Figure 1b), as well as a higher P_{es} and RPP (Table 2) as indications of end systolic arterial pressure and myocardial oxygen consumption, respectively. These results are consistent with previous findings of heightened myocardial stress following infection with SARS-CoV-2 (Bavishi et al., 2020). Further indications of a heightened autonomic response such as a higher SBP and CI to HG exercise in the current investigation and various other stimuli (Shouman et al., 2021) provide additional evidence of exaggerated haemodynamic responses to stress among those with acute SARS-CoV-2 infection. More work is needed to determine the potential lasting impact of such alterations on cardiovascular responses to exercise.

While central limitations to exercise are concerning for those recovering from SARS-CoV-2, it is important to make distinctions between peripheral and central contributions to exercising haemodynamics to discern potential impairments that may contribute to whole body limitations. Indeed, given that ACE2 is expressed by endothelial cells, increased peripheral resistance may be responsible for augmented blood pressures accompanying roughly 30% of those diagnosed with SARS-CoV-2 (Schiffrin et al., 2020). Accordingly, the decrement in vascular function following SARS-CoV-2 infection, which impacts a wide range of persons with varying symptom severities (Ratchford et al., 2021; Riou et al., 2021), deserves further investigation.

4.2 | Exercising peripheral haemodynamics in SARS-CoV-2

Several accounts of diminished exercise capacity have emerged in response to severe SARS-CoV-2 infection (Baratto *et al*., 2021; Dorelli *et al*., 2021; Huang et al., 2021; Raman et al., 2021), yet little is known of whether these limitations may be centrally or peripherally mediated. Our group (Ratchford et al., 2021) and others (Riou et al., 2021) have recently established acute vascular impairments at rest in adults recovering from symptomatic to critical cases of SARS-CoV-2, which may translate to diminished vascular function during exercise. Indeed, vascular contributions to exercise capacity have recently been suggested to outweigh respiratory and cardiac limitations in survivors of severe SARS-CoV-2 (Baratto *et al*., 2021).

While central factors may limit whole-body exercise performance, small muscle mass exercise modalities like rhythmic HG exercise often are limited by local factors that regulate exercising BF. Further, the use of Doppler ultrasound in conjunction with beat-by-beat blood pressure measures provides a unique opportunity to assess oscillatory BF and vascular conductance patterns, which may help discern potential limitations to exercising BF among anterograde and retrograde BF. Similar to our current results, previous reports have revealed a minimal contribution of retrograde BF to mean brachial artery BF changes during progressive HG exercise in healthy adults (Green et al., 2005). While chronic diseases such as hypertension (Thomas, 2015) or heart failure with reduced ejection fraction (Benda et al., 2015) may result in heightened retrograde BF during exercise, systemic inflammatory conditions such as Kawasaki disease have revealed a time-dependent relationship of prolonged disease on increases in retrograde BF (Mori et al., 2000). While the current investigation only assessed young adults with SARS-CoV-2 3–4 weeks after testing positive for the infection, perhaps time since infection, exercise duration, mode of exercise and age of the subjects may be factors in the discrepancy between our results and those in chronic diseases such as heart failure. Regardless of the precise mechanism, the lower aFBF without a significant change to rFBF among adults with SARS-CoV-2 compared with healthy adults (Figure 2) may be useful in identifying the specific oscillatory BF pattern following infection, as well as serve as a potential therapeutic target in the future.

In the current investigation, our findings of decreased FBF in the SARS-CoV-2 group (Figure 2c) certainly could be due to a host of local and systemic factors. The cytokine storm that accompanies viral propagation of SARS-CoV-2 is likely a primary cause for decreased exercising FBF. Other variables such as blood viscosity (Joob & Wiwanitkit, 2021) may additionally impact the vasculature and FBF. Several studies have reported higher incidence of arterial and venous thrombosis in patients with SARS-CoV-2, which may be the results of venous stasis, increased inflammation-induced coagulation and subsequent vascular damage (Ahmed et al., 2020; Demelo-Rodriguez et al., 2020; Lodigiani et al., 2020; Middeldorp *et al*., 2020; Wichmann et al., 2020).

Further, while it is unknown whether metaboreflex, mechanoreflex or baroreflex sensitivity is altered due to a heightened inflammatory state in SARS-CoV-2, heightened sympathetic outflow, wherein vasoconstriction would limit FBF, may also exacerbate the vascular response to exercise (Prabhakar & Kumar, 2010). This systemic, sympathetically mediated microvasculature vasoconstriction may partially explain the lower FBF among the SARS-CoV-2 group. While BF may be impacted by driving pressures, the lower vascular conductance response to HG exercise among adults with SARS-CoV-2 (Table 3) further corroborates the notion of peripheral haemodynamic limitations during exercise despite a heightened SBP response during exercise. Together, these results provide evidence for diminished microvascular responses to small muscle mass exercise among adults recently infected with SARS-CoV-2. Given the multitude of vascular regulators during exercise (Hellsten et al., 2012) as well as the potential for a compounding impact of systemic inflammation, multiple factors may be responsible for decreased exercising BF among young adults with SARS-CoV-2.

Ultimately, the lower BF response to exercise could contribute to lower exercise capacity, as has been suggested in several disease states (Poole et al., 2021). Given the well-known heterogeneity between the lower and upper extremity vascular regulation to exercise (Newcomer et al., 2005; Nishiyama *et al*., 2008; Richardson et al., 2006; Wray & Richardson, 2006; Wray *et al*., 2005), future studies should investigate the potential exercising BF characteristics among adults with SARS-CoV-2 in the lower extremity and whether a lower hyperaemic response may be accompanied by higher oxygen extraction.

4.3 | Endothelium-dependent vasodilatation during handgrip exercise in SARS-CoV-2

The HG exercise modality in the current investigation offered the opportunity to evaluate the stimulus–response relationship between graded increases in shear stress and the subsequent brachial artery vasodilatation through progressive increases in exercise intensity, ultimately allowing a more comprehensive examination of potential disease-related changes in endothelium-dependent vasodilatation. While FMD is typically determined as the increase in conduit vessel diameter following a period of circulatory occlusion and tissue ischaemia, this approach offers only a single data point during rest. A much lengthier protocol would be required to evaluate brachial artery vasodilatation across a range of occlusion times and associated shear stimuli. Further, while the magnitude of brachial artery FMD was previously thought to be predominantly nitric oxide (NO) mediated (Joannides et al., 1995), this concept has more recently been called into question (Pyke et al., 2010; Wray et al., 2013), further exemplifying the need for alternative approaches for the assessment of endothelial function. Several groups (Donato et al., 2010; Machin et al., 2016; Richardson et al., 2007; Tremblay & Pyke, 2018; Trinity et al., 2013) have established the use of rhythmic HG exercise as an experimental model to expose the brachial artery to step-wise increases in 'sustained stimulus FMD' (SS-FMD) (Tremblay & Pyke, 2018), which appears to be a largely NO-dependent process (Wray et al., 2011). Given the evidence suggesting that transient and sustained shear may be transduced differently across the endothelium (Frangos et al., 1996) and recent work suggesting an increased sensitivity of SS-FMD over traditional FMD testing to detect endothelial dysfunction in patient groups (Bellien et al., 2010; Grzelak et al., 2010; Ratchford *et al*., 2020), the current study utilized the SS-FMD to further evaluate endothelial function in adults with SARS-CoV-2. While the shear stimulus response was greater in the control group, the shear-induced vasodilatation was similar between groups (Figure 3), suggesting similar SS-FMD responses between groups and similar conduit vessel function during exercise. Viewed in conjunction with the observed attenuation in forearm BF (Figure 2c) and vascular conductance (Table 3) during exercise, these results provide further evidence for a decline in vascular function at the level of the smaller resistance vasculature during exercise, but not the conduit arteries in adults with SARS-CoV-2. These findings extend our previous work which provided evidence of diminished microvascular function in the lower extremities, yet contradictorily provided evidence of reduced FMD in the conduit vessel and lack of microvascular impairment in the upper extremity during rest (Ratchford et al., 2021), which may be due in part to various alterations to the metabolic milieu beyond NO at traditional FMD during rest as opposed to SS-FMD during HG exercise.

4.4 | Experimental considerations

There are several potential limitations to the current investigation. We recognize the limitations to a cross-sectional analysis such as this, despite the common use of such an experimental design among infectious disease studies. Further, despite several investigations failing to identify sex-specific differences in exercising BF of healthy adults, especially when matched for absolute workload (Hill et al., 2018; Hunter et al., 2009; Limberg *et al*., 2010), sex-specific exercising BF changes may occur among those afflicted with SARS-CoV-2 and should be taken into consideration in larger cohort studies. Given the unusual circumstances of research during COVID-19 restrictions, including accommodating quarantine procedures, we chose not to control for the menstrual cycle in our female participants, which may have resulted in many of our female subjects being outside of the 3–4 week post-positive PCR test inclusion criteria. Additionally, as the control group was on average 6 years older than the SARS-CoV-2 group, differences in exercising BF may be masked by the subtle age-related decline in exercising BF seen in ageing populations (Donato et al., 2006; Proctor & Parker, 2006). In the present study, we chose not to normalize limb BF for muscle mass, but acknowledge that this approach may limit application of our findings in cohorts where large variations in limb volume are present. Further, physical activity and exercise training can certainly impact vascular health and responses to exercise (Narici et al., 2021). While our group cohorts consisted of a mix of recreationally active and inactive individuals, we did not consistently characterize previous physical activity levels using a standardized questionnaire between all subjects, which we recognize

as a potential limitation in interpreting these findings to physically active and/or inactive individuals. Further, given the heterogeneity of vascular responses in upper and lower extremities (Newcomer et al., 2005), care should be taken when translating these observations to lower extremity exercise haemodynamics. Finally, we also chose to focus on steady-state haemodynamics during HG exercise, which precludes investigation of potential differences in on- and off-kinetics of central and peripheral haemodynamics between groups, which may be considered in future investigations.

4.5 | Conclusion

This investigation has identified, for the first time, a reduction in exercising skeletal muscle BF and vascular conductance during rhythmic HG exercise in young adults with SARS-CoV-2 compared with healthy young adults. This reduction in exercising BF may contribute to the exercise intolerance that can accompany COVID-19 and should be considered for rehabilitation efforts following SARS-CoV-2 infection.

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COMPETING INTERESTS

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

A.S.L.S., J.L.S. and S.M.R. conceived and designed research; N.L.S., V.M.P., M.A.A., J.L.S., K.B., J.K.A., D.W.W., A.S.L.S. and S.M.R. performed experiments; N.L.S. and S.M.R. analysed data; N.L.S., V.M.P., M.A.A., K.B., J.K.A., D.W.W., A.S.L.S., J.L.S. and S.M.R. interpreted results of experiments; N.L.S. and S.M.R. prepared figures; N.L.S. and S.M.R. drafted manuscript; N.L.S., V.M.P., M.A.A., K.B., J.K.A., D.W.W., A.S.L.S., J.L.S. and S.M.R. 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.

DATA AVAILABILITY STATEMENT

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

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