

RESEARCH PAPER

Carotid stiffness, intima-media thickness and aortic augmentation index among adults with SARS-CoV-2

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Edited by: Robert Brothers

Abstract

Contracting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been observed to cause decrements in vascular function of young adults. However, less is known about the impact of SARS-CoV-2 on arterial stiffness and structure, which might have additional implications for cardiovascular health. The purpose of this study was to assess the carotid artery stiffness and structure using ultrasound and the aortic augmentation index (AIx) using applanation tonometry in young adults after they tested positive for SARS-CoV-2. We hypothesized that carotid artery stiffness, carotid intima-media thickness (cIMT) and aortic AIx would be elevated in young adults with SARS-CoV-2 compared with healthy young adults. We evaluated 15 young adults (six male and nine female; 20 ± 1 years of age; body mass index, 24 ± 3 kg m⁻²) 3–4 weeks after a positive SARS-CoV-2 test result compared with young healthy adults (five male and 10 female; 23 ± 1 years of age; body mass index, 22 ± 2 kg m⁻²) who were evaluated before the coronavirus 2019 pandemic. Carotid stiffness, Young's modulus and cIMT were assessed using ultrasound, whereas aortic AIx and aortic AIx standardized to 75 beats min⁻¹ (AIx@HR75) were assessed from carotid pulse wave analysis using SphygmoCor. Group differences were observed for carotid stiffness (control, 5 ± 1 m s⁻¹; SARS-CoV-2, 6 ± 1 m s⁻¹), Young's modulus (control, 396 ± 120 kPa; SARS-CoV-2, 576 ± 224 kPa), aortic AIx (control, $3 \pm 13\%$; SARS-CoV-2, $13 \pm 9\%$) and aortic AIx@HR75 (control, $-3 \pm 16\%$; SARS-CoV-2, $10 \pm 7\%$; $P < 0.05$). However, cIMT was similar between groups (control, 0.42 ± 0.06 mm; SARS-CoV-2, 0.44 ± 0.08 mm; $P > 0.05$). This cross-sectional analysis revealed higher carotid artery stiffness and aortic stiffness among young adults with SARS-CoV-2. These results provide further evidence of cardiovascular impairments among young adults recovering from SARS-CoV-2 infection, which should be considered for cardiovascular complications associated with SARS-CoV-2.

KEYWORDS

aortic augmentation index, carotid stiffness, COVID-19, intima-media thickness, SARS-CoV-2

1 | INTRODUCTION

In March of 2020, transmission of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a pandemic by the World Health Organization. Given that SARS-CoV-2 initially attacks cells within the nasal cavity, upper and conducting airways and the pulmonary parenchyma, clinical presentations include mild symptoms akin to an upper respiratory tract infection, pneumonia and/or acute respiratory distress syndrome (Pirzada et al., 2020). However, consequences are not limited only to the respiratory system. In fact, decrements abound in the downstream physiological systems, including the nervous system, kidneys and the vasculature (Clerkin et al., 2020; Montalvan et al., 2020; Ratchford et al., 2020).

SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor, downregulating ACE2 expression and prohibiting the protective effects of the enzyme within several tissues, including the heart and blood vessels (Monteil et al., 2020). SARS-CoV-2 infection can, therefore, lead to damage of the myocardium and vascular endothelium (Evans et al., 2020; Pirzada et al., 2020; Siripanthong et al., 2020; Tadic et al., 2020). In addition to ACE2-related impairments in the vascular endothelium, the systemic cytokine-induced inflammatory response (Channappanavar & Perlman, 2017; Coperchini et al., 2020) caused by viral detection and propagation could also have further prolonged, deleterious, effects downstream of the initial viral parasitism of SARS-CoV-2 in the lung (Li, Hao et al., 2020). The combination of ACE2 inhibition along with heightened inflammation and oxidative stress can evoke alterations to vascular function, and potential structural alterations might be seen in the form of arterial stiffness. This acute inflammatory response can cause alterations to carotid stiffness and carotid intima-media thickness (cIMT), akin to those typically observed after acute bacterial and viral infections (Çiftel et al., 2014; Ibrahim et al., 2016; Wu et al., 2014), in addition to vaccination treatments (Vlachopoulos et al., 2005) and various inflammatory states (Roman et al., 2005; Zanolli, Boutouyrie et al., 2017; Zanolli, Granata et al., 2017; Zanolli et al., 2020). These observational studies from acute infectious agents highlight the potential for cIMT and other structural indices throughout the arterial tree to change acutely among individuals experiencing heightened infection-related inflammation. Indeed, several infectious agents, including *Chlamydia pneumoniae*, *Porphyromonas gingivalis*, *Helicobacter pylori*, cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus, herpes simplex virus-1 and hepatitis C virus, have been implicated in promoting endothelial cell inflammation and macrophage formation and inhibiting smooth muscle cell apoptosis (Li, Xia et al., 2020). Together, these mechanisms for vascular alterations have potential implications for vascular health, progression of atherosclerosis, and cardiovascular event risk (Tobayama et al., 2013), which might be impacted by SARS-CoV-2.

Our group has previously provided evidence of vascular dysfunction after SARS-CoV-2 infection, as evidenced by lower brachial artery flow-mediated dilatation and lower hyperaemic response to passive limb movement, in addition to an elevated peripheral carotid-femoral pulse wave velocity among young adults with SARS-CoV-2 compared

New Findings

- **What is the central question of this study?**

We sought to investigate whether carotid stiffness, carotid intima-media thickness and the aortic augmentation index are altered in young adults 3–4 weeks after contraction of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) compared with young healthy adults.

- **What is the main finding and its importance?**

We found that carotid stiffness, Young's modulus and the aortic augmentation index were greater in young adults who tested positive for SARS-CoV-2 compared with healthy young adults. These findings provide additional evidence for detrimental effects of SARS-CoV-2 on young adult vasculature, which might have implications for cardiovascular health.

with healthy control subjects (Ratchford et al., 2020). Likewise, a recent study using the rudimentary measure of pulse pressure as an arterial stiffness index has revealed an association between pulse pressure and all-cause mortality in patients with SARS-CoV-2 (Rodilla et al., 2021). These data suggest an impairment in vascular regulation, which might predispose individuals to a greater risk of cardiovascular disorders, such as myocardial injury, arrhythmias, acute coronary syndrome or thromboembolism (Driggin et al., 2020). Indeed, cardiovascular symptoms can manifest without typical flu-like symptoms of SARS-CoV-2 infection (Deng et al., 2020; Stefanini et al., 2020), with myocardial injury independently being associated with high mortality during the course of the disease (Shi et al., 2020). Although cardiovascular disease ranks among the top comorbid conditions associated with SARS-CoV-2-related morbidity (Wu & McGoogan, 2020), little is known regarding how SARS-CoV-2 might alter other arterial factors associated with premature atherosclerosis, a heightened cardiovascular event risk and all-cause mortality (Vlachopoulos et al., 2010), specifically carotid artery stiffness, carotid distensibility, cIMT and aortic augmentation index (AIx), which typically reflect changes to arterial structure compared with previously observed vascular alterations.

Therefore, the primary aim of this investigation was to examine whether carotid artery stiffness, carotid distensibility, cIMT and aortic AIx are altered in young adults after contraction of SARS-CoV-2 while using a cross-sectional study design for comparison with young healthy adults. We hypothesized that carotid stiffness indices would be greater in the SARS-CoV-2 group, as reflected by changes in stiffness, distensibility, compliance and Young's modulus (Butlin & Qasem, 2017; Kim & Kim, 2019). We also hypothesized that cIMT would be greater in the SARS-CoV-2 group, providing a preclinical index of atherogenesis. Furthermore, we hypothesized

greater indices of aortic augmentation in the SARS-CoV-2 group, indicated by the central haemodynamic measures derived from carotid pulse wave analysis (PWA), including aortic AIx and aortic AIx standardized for a heart rate for 75 beats min^{-1} (AIx@HR75). As a secondary aim, we sought to identify whether indices for myocardial oxygen demand and perfusion were altered in young adults after contraction of SARS-CoV-2 compared with young healthy adults. We hypothesized the SARS-CoV-2 group would have a greater myocardial stress response, derived from PWA, as indicated by the diastolic to systolic pressure–time integral as indices of myocardial oxygen demand and perfusion, further suggesting that these vascular alterations might have implications for overall cardiovascular health.

2 | METHODS

2.1 | Ethical approval

All procedures were approved by the Appalachian State University Institutional Review Board (IRB_20-0304 and IRB_20-0151). The study conformed to the standards set by the *Declaration of Helsinki*, except for registration in a database. Before testing, experimental procedures were explained to participants, both in writing and verbally, and subjects provided written informed consent.

2.2 | Subjects

The inclusion criteria for subjects included relatively healthy young adults free from chronic metabolic, cardiovascular and pulmonary disease. Female subjects were premenopausal and not pregnant or trying to become pregnant. Potential subjects were excluded if they were smokers, had any orthopaedic limitations and were taking any medications known to alter vascular function, such as ACE inhibitors or diuretics. Potential subjects were also excluded if they were hospitalized owing to the virus. On 4–6 February 2020, which was before the first confirmed case of coronavirus disease 2019 (COVID-19) in North Carolina, USA on 3 March 2020 and before the World Health Organization declared COVID-19 a pandemic (NC Department of Health and Human Services, 2020), subjects in the control group were studied. Control subjects did not report any flu-like symptoms. Subjects included in the SARS-CoV-2 group tested positive for SARS-CoV-2 using a nasopharyngeal swab PCR assay 3–4 weeks before study testing.

2.3 | Study procedures

Before testing, subjects completed a health history questionnaire, detailing personal and family medical history, the frequency and duration of physical activity and any medication usage. Subjects arrived for testing in a fasted state having abstained from food and caffeine for 12 h and from exercise and alcohol for 24 h before testing. All study

procedures were performed in a quiet, thermoneutral environment after subjects had lain supine for 20 min. For standardization purposes, study procedures were ordered in a similar manner between subjects.

2.4 | COVID-19 symptom severity survey

Subjects who tested positive for SARS-CoV-2 were asked to rank their COVID-19 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 $>37.9^{\circ}\text{C}$, 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 34–66 and severe 67–100.

2.5 | Experimental measurements

After 20 min of supine rest, an automated brachial artery cuff was used to determine supine blood pressures (EVOLV, Omron Healthcare, Kyoto, Japan) before carotid stiffness, cIMT and PWA measurements. All measurements were taken on the right side of the body among all subjects.

2.6 | Carotid stiffness

Subsequent to supine blood pressure measurements, subjects remained supine for assessment of carotid stiffness using an ultrasound system (12L-RS Linear Array Probe, GE Logiq eR7; GE Medical Systems, Milwaukee, WI, USA) over the common carotid artery, ≥ 1 –2 cm proximal to the bifurcation, with an imaging frequency between 4 and 12 MHz in B-mode. Between 10 and 15 cardiac cycles were recorded and analysed by a single operator with CAROTID STUDIO (Cardiovascular Suite, Qipu srl, Pisa, Italy) to obtain measurements for stiffness using the Bramwell–Hill equation, distensibility, compliance and Young's modulus (Bruno et al., 2017), where D_s is the external systolic diameter, D_i is the internal diastolic diameter, and D_d is the external diastolic diameter between the media–adventitia interfaces. Systolic and diastolic diameters were determined as the largest and smallest diameters, respectively, obtained during real-time playback of the ultrasound recording. The D_i is the internal diastolic diameter between the lumen–intima interfaces, P_s is the brachial systolic pressure, P_d is the brachial diastolic pressure, and ρ is the blood density constant of 1.05 g cm^{-3} :

$$\text{Carotid stiffness (ms}^{-1}\text{)} = \sqrt{\frac{D_d^2(P_s - P_d)}{\rho(D_s^2 - D_i^2)}}$$

$$\text{Distensibility } (10^{-3} \text{ kPa}^{-1}) = \frac{1}{D_d^2} \times \frac{D_s^2 - D_d^2}{P_s - P_d}$$

$$\text{Compliance } (\text{mm}^2 \text{ kPa}^{-1}) = \frac{\pi}{4} \times \frac{D_s^2 - D_d^2}{P_s - P_d}$$

$$\text{Young's modulus (kPa)} = \frac{3}{\text{Distensibility}} \times \left[1 + \frac{\frac{\pi}{4} \times D_d^2}{\frac{\pi}{4} \times (D_s^2 - D_d^2)} \right]$$

Carotid stiffness is considered an important index positively associated with the pathogenesis of cardiovascular disease. Carotid distensibility measures the carotid artery elasticity, which is negatively associated with cardiovascular disease (Godia et al., 2007). Carotid compliance is the reciprocal of stiffness and is negatively associated with cardiovascular disease (Van Merode et al., 1990). Young's modulus differs from compliance and distensibility in that the wall thickness is incorporated for its determination, thus providing a more integrated assessment of arterial circumferential stretching, which has been positively associated with age-related atherosclerosis (Riley et al., 1992).

2.7 | Carotid diameters and intima-media thickness

Using the same 10–15 cardiac cycles used to measure carotid stiffness, the systolic, diastolic and mean carotid diameters and cIMT were measured and analysed using CAROTID STUDIO. Systolic, diastolic and mean carotid diameters were determined as the largest, smallest and average diameters obtained, respectively, of the interior, luminal diameters during each cardiac cycle measured from the ultrasound recordings. The cIMT was measured as the distance from the lumen-intima interface to the media-adventitia interface using the deep wall of the carotid artery to calculate the mean cIMT over the recorded 10–15 cardiac cycles. Once the media-adventitia borders were validated by the operator, the lumen-intima boundaries were detected automatically by the software and adjusted by the operator as necessary.

2.8 | Carotid pulse wave analysis

A SphygmoCor CPv (AtCor Medical, Sydney, Australia) device was used to record carotid PWA via applanation tonometry. The probe was positioned over the common carotid artery. After 20 sequential waveforms were recorded, the intrinsic transfer function of the SphygmoCor generated average peripheral waveforms (Wilkinson et al., 1998). From these waveforms, central haemodynamic parameters were estimated using the general transfer function, including the aortic augmentation index (AIx), aortic augmentation pressure (AP), central pressures (systolic, diastolic, pulse and mean arterial blood pressures), heart rate period, duration of the wave-

form to reach peak pressure (aortic T2), pressure obtained at the first peak/shoulder (P1 height), end-systolic pressure, mean systolic pressure and mean diastolic pressure. Systolic blood pressure was identified as the height of the first peak in the waveform, whereas diastolic blood pressure was identified as the value at the foot of the waveform. End-systolic pressure was identified as the pressure at the end of the first peak in the waveform. The pulse pressure was calculated as the difference between systolic and diastolic pressures. Mean systolic pressure was defined as the average pressure between the beginning of the waveform and the end of the first peak, whereas mean diastolic pressure was defined as the average pressure from the end of the first peak to the end of the waveform. The AIx was defined as augmentation pressure relative to pulse pressure expressed as a percentage, where aortic AP was calculated as the difference between the first and second systolic pressure peaks of the waveform (Wilkinson et al., 2000, 2002). To standardize AIx for a heart rate of 75 beats min^{-1} , the following equation was used:

$$\text{AIx@HR75(\%)} = \text{AIx} - 0.39(75 - \text{HR})$$

2.9 | Indices of myocardial oxygen demand and perfusion

During the PWA, the Buckberg subendocardial viability ratio (SERV) was determined as the ratio between diastolic pressure-time index (DPTI) and the systolic pressure-time index (SPTI), defined as the areas under the pulse pressure during diastole and systole (Scandale et al., 2018). Ejection duration was measured as the period of time (in milliseconds) from the beginning of the waveform to the incisura (Wilkinson et al., 2000).

2.10 | Statistical analysis

Statistics were performed using commercially available software (IBM SPSS Statistics v.26, Armonk, NY, USA). Student's two-tailed t-tests for two samples of equal variance were performed between the control and SARS-CoV-2 groups. Data were checked for normality using the Shapiro-Wilk test and boxplots. Statistical significance was specified at $P < 0.05$. Hedge's g was measured as an indicator of effect size, because a value of one indicates that the two groups differ by one standard deviation, or a value of two indicates that the groups differ by two standard deviations. Subject characteristics and outcome measures are expressed as the mean \pm SD.

3 | RESULTS

3.1 | Subject characteristics

The control group consisted of five male and 10 female adults, whereas the experimental group consisted of six male and nine female

TABLE 1 Subject characteristics

Characteristics	Control (5 male, 10 female)	SARS-CoV-2 (6 male, 9 female)	P-value	Hedge's <i>g</i>
Subjects (<i>n</i>)	15	15	–	–
Age (years)	23 ± 1	20 ± 1	<0.01	2.01
Height (cm)	168 ± 10	172 ± 11	0.48	–0.38
Weight (kg)	63 ± 7	71 ± 13	0.11	–0.71
Body mass index (kg m ^{–2})	22 ± 2	24 ± 3	0.23	–0.51
Physical activity				
Frequency (days week ^{–1})	4 ± 2	4 ± 1	0.72	0.12
Duration (min day ^{–1})	44 ± 15	41 ± 12	0.77	0.25
Female contraceptive use (<i>n</i>)	4	5	0.44	–0.54

Data are the mean ± SD. Student's two-tailed *t*-tests for two samples of equal variance were performed between control and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) groups.

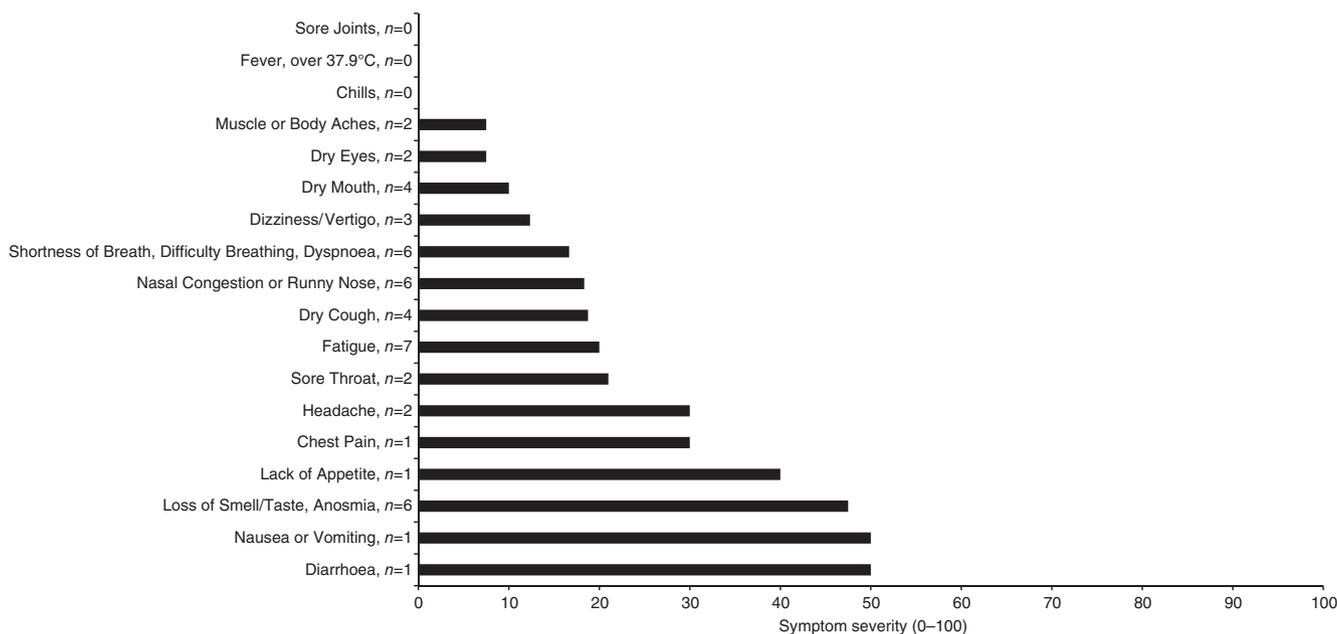


FIGURE 1 Severity of coronavirus disease 2019 symptoms. Subjects with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) self-reported symptom severity on a scale of 0–100, with increasing severity, on the day of testing (*n* = 6 male and 8 female). One female subject with SARS-CoV-2 was asymptomatic and excluded from the figure. Data are the mean among individuals with SARS-CoV-2 symptoms

adults who tested positive for SARS-CoV-2. Subject characteristics are detailed in Table 1. In general, subjects were well matched for height, weight, physical activity and contraceptive use. Both groups were predominately Caucasian, except for one female subject in the control group whose ethnicity was Hispanic, Latino and one female subject in the SARS-CoV-2 group who was Asian. Subjects were otherwise free from medication usage. Although one female subject with SARS-CoV-2 was asymptomatic, subjects who tested positive for SARS-CoV-2 were tested 25 ± 5 days after symptom onset (*n* = 6 male and 8 female) and 24 ± 6 days after a positive SARS-CoV-2 PCR test result (*n* = 6 male and 9 female).

3.2 | SARS-CoV-2 symptom severity

Among the subjects who tested positive for SARS-CoV-2, 14 subjects (6 male and 8 female) had mild symptoms at the time of testing (Figure 1). Seven subjects had fatigue; six subjects had a loss of smell, nasal congestion or shortness of breath; four subjects had dry cough or dry mouth; three subjects had dizziness or vertigo; and two subjects had dry eyes, a headache, muscle or body aches or a sore throat. Overall, subjects had 3.2 ± 2.1 symptoms among the 18 symptoms surveyed, and the severity of these symptoms averaged 19 ± 13 out of 100 of increasing severity.

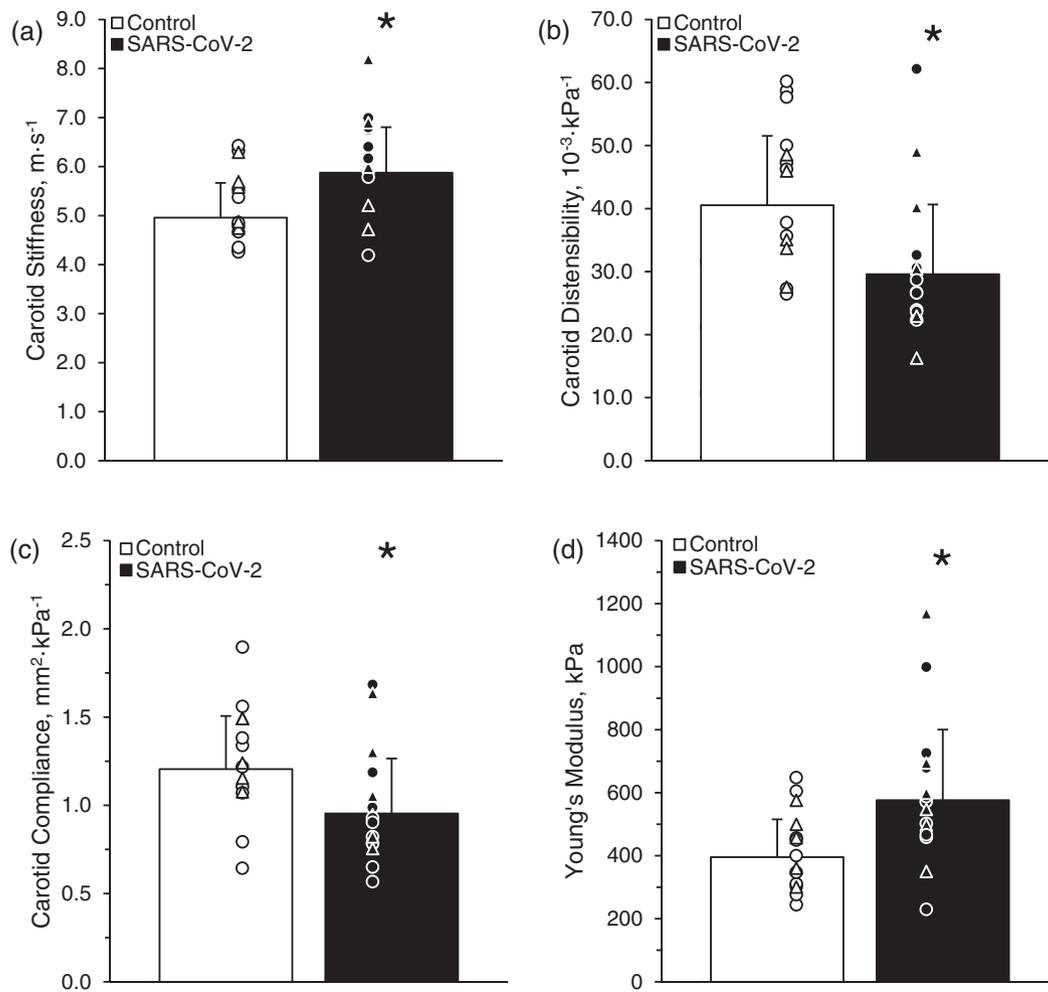


FIGURE 2 Carotid stiffness (a), distensibility (b), compliance (c) and carotid Young's modulus of elasticity (d) in control subjects and subjects who tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Student's two-tailed *t*-tests for two samples of equal variance were performed between the control ($n = 5$ male and 10 female) and SARS-CoV-2 ($n = 6$ male and 9 female) groups. * $P < 0.05$, between groups. Individual data are presented as open triangles (male subjects) and circles (female subjects) for the control group and filled triangles and circles for the SARS-CoV-2 group. Data are the mean \pm SD

3.3 | Carotid stiffness

Carotid stiffness was greater in the SARS-CoV-2 group ($6 \pm 1 m s^{-1}$) compared with the control group ($5 \pm 1 m s^{-1}$; $P = 0.02$, Hedge's $g = -1.08$; Figure 2a). Carotid distensibility was lower in the SARS-CoV-2 group ($30 \times 10^{-3} \pm 12 \times 10^{-3} kPa^{-1}$) compared with the control group ($40 \times 10^{-3} \pm 11 \times 10^{-3} kPa^{-1}$; $P = 0.01$, Hedge's $g = 0.97$; Figure 2b). Carotid compliance was lower in the SARS-CoV-2 group ($0.97 \pm 0.33 mm^2 kPa^{-1}$) compared with the control group ($1.20 \pm 0.31 mm^2 kPa^{-1}$; $P = 0.03$, Hedge's $g = 0.80$; Figure 2c). Young's modulus of elasticity in the carotid artery was greater in the SARS-CoV-2 group ($0.59 \pm 0.24 kPa$) compared with the control group ($0.40 \pm 0.12 kPa$; $P = 0.01$, Hedge's $g = -0.98$; Figure 2d).

3.4 | Carotid diameters and intima-media thickness

Measurements of carotid diameters and cIMT are detailed in Table 2. Generally, carotid diameters and cIMT were unaltered among adults with SARS-CoV-2 compared with healthy adults, although carotid systolic diameter was greater among adults with SARS-CoV-2 compared with healthy adults ($P = 0.049$).

3.5 | Carotid pulse wave analysis

Peripheral and central blood pressures and carotid PWA measures (heart rate period, aortic T2, P1 height, aortic AP and aortic Alx)

TABLE 2 Carotid diameters and intima-media thickness

Parameter	Control (5 male, 10 female)	SARS-CoV-2 (6 male, 9 female)	P-value	Hedge's <i>g</i>
Mean diameter (mm)	6.48 ± 0.49	6.78 ± 0.57	0.13	-0.55
Diastolic diameter (mm)	6.31 ± 0.53	6.46 ± 0.55	0.45	-0.27
Systolic diameter (mm)	6.64 ± 0.57	7.07 ± 0.59	<0.05	-0.73
cIMT (mm)	0.42 ± 0.06	0.44 ± 0.08	0.59	-0.19

Data are the mean ± SD. Student's two-tailed *t*-tests for two samples of equal variance were performed between the control and SARS-CoV-2 groups. Abbreviations: cIMT, carotid intima-media thickness; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

TABLE 3 Central pressures and carotid pulse wave analysis measures

Parameter	Control (5 male and 10 female)	SARS-CoV-2 (6 male and 9 female)	P-value	Hedge's <i>g</i>
Peripheral carotid pressures				
Peripheral systolic pressure (mmHg)	121 ± 12	129 ± 13	0.09	-0.63
Peripheral diastolic pressure (mmHg)	70 ± 8	74 ± 7	0.20	-0.47
Peripheral pulse pressure (mmHg)	51 ± 9	55 ± 10	0.20	-0.47
Peripheral mean arterial pressure (mmHg)	87 ± 10	99 ± 8	<0.01	-1.17
Central aortic pressures				
Central systolic pressure (mmHg)	109 ± 14	124 ± 11	<0.01	-1.20
Central diastolic pressure (mmHg)	70 ± 9	74 ± 7	0.22	-0.45
Central pulse pressure (mmHg)	38 ± 12	50 ± 7	<0.01	-1.63
Central mean arterial pressure (mmHg)	85 ± 11	99 ± 8	<0.01	-1.39
Pulse wave analysis				
Heart rate period (ms)	1,004 ± 235	898 ± 150	0.15	0.52
Ejection duration (ms)	333 ± 14	316 ± 17	0.01	1.07
Ejection duration (%)	35 ± 7	36 ± 4	0.55	-0.22
Aortic T2	219 ± 22	217 ± 44	0.82	0.08
P1 Height (P1 - DP)	34 ± 12	44 ± 8	0.02	-0.90
Aortic augmentation pressure (mmHg)	1.0 ± 5.7	6.2 ± 4.7	0.01	-0.97
Aortic Alx (P2/P1; %)	108 ± 13	116 ± 12	0.07	-0.67
Buckberg SEVR (%)	162 ± 44	146 ± 27	0.25	-0.41
SPTI (mmHg s min ⁻¹)	2,099 ± 447	2,429 ± 368	0.04	-0.78
DPTI (mmHg s min ⁻¹)	3,239 ± 453	3,476 ± 333	0.12	-0.58
End systolic pressure (mmHg)	98 ± 12	107 ± 9	0.03	-0.82
Mean systolic pressure (mmHg)	101 ± 10	113 ± 10	<0.01	-1.12
Mean diastolic pressure (mmHg)	83 ± 9	90 ± 7	0.02	-0.87

Data are the mean ± SD. Student's two-tailed *t*-tests for two samples of equal variance were performed between the control (and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) groups. Abbreviations: Alx, augmentation index; DP, diastolic pressure; DPTI, diastolic pressure-time index; P1, first systolic peak; P2, second systolic peak; SEVR, subendocardial viability ratio; STPI, systolic pressure-time index; T2, duration from the start of the pulse to the second systolic peak.

are detailed in Table 3. Peripheral carotid mean arterial pressure along with the central aortic systolic, pulse and mean arterial pressures were greater in the SARS-CoV-2 group compared with the control group. Aortic augmentation pressure was greater in the SARS-CoV-2 group compared with the control group. Mean systolic and diastolic pressures were greater in the SARS-CoV-2 group compared

with the control group (Table 3). Aortic Alx was greater in the SARS-CoV-2 group (12.7 ± 9.1%) compared with the control group (3.3 ± 12.6%; *P* = 0.03, Hedge's *g* = -0.82; Figure 3a). Aortic Alx@HR75 was greater in the SARS-CoV-2 group (9 ± 7%) compared with the control group (-3 ± 17%; *P* = 0.01, Hedge's *g* = -1.00; Figure 3b).

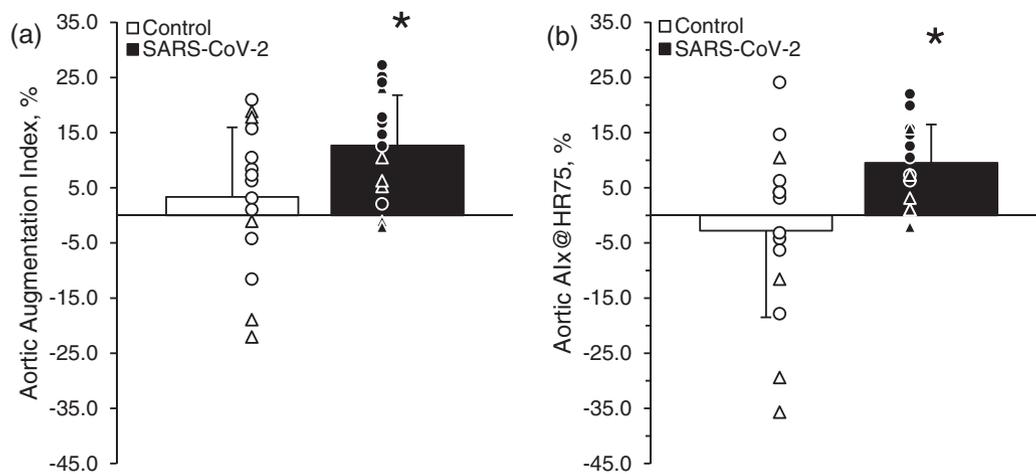


FIGURE 3 Aortic augmentation index (a) and aortic augmentation index corrected for a heart rate of 75 beats min^{-1} (Alx@HR75; b) in control subjects and subjects who tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Student's two-tailed t-tests for two samples of equal variance were performed between the control ($n = 5$ male and 10 female) and SARS-CoV-2 ($n = 6$ male and 9 female) groups. * $P < 0.05$, between groups. Individual data are presented as open triangles (male subjects) and circles (female subjects) for the control group and filled triangles and circles for the SARS-CoV-2 group. Data are the mean \pm SD

3.6 | Indices of myocardial oxygen demand and perfusion

Indices of myocardial oxygen demand and perfusion, including Buckberg SEVR, SPTI, DPTI and ejection duration, are detailed in Table 3. The SPTI was ~16% greater ($P = 0.04$) and the ejection duration 17 ms faster ($P = 0.01$) in the SARS-CoV-2 group compared with the control group.

4 | DISCUSSION

The aim of this study was to investigate whether carotid artery stiffness, carotid distensibility, cIMT and aortic Alx are altered in young adults after contraction of SARS-CoV-2 compared with young healthy adults using a cross-sectional design. In support of our hypotheses, we observed less carotid compliance and distensibility among young adults who recently contracted SARS-CoV-2 compared with healthy control adults. Furthermore, we observed greater carotid stiffness and Young's modulus among individuals with SARS-CoV-2 compared with healthy controls. We observed a greater aortic Alx and Alx@HR75, which also suggests aortic stiffening and potential atherosclerotic risk progression. However, we did not observe any difference in cIMT. As a secondary objective, we determined the potential change among indices of myocardial oxygen demand and perfusion. In partial support of our secondary hypothesis, SPTI was elevated and ejection duration lower among individuals with SARS-CoV-2, suggesting minor elevations in myocardial oxygen demand and further evidence of arterial stiffness among adults recovering from SARS-CoV-2. Ultimately, these data suggest altered arterial stiffness among young adults who have recently contracted SARS-CoV-2, which might negatively influence cardiovascular health. Furthermore, these

findings might have potential implications for future cardiovascular complications caused by SARS-CoV-2.

4.1 | Carotid stiffness with SARS-CoV-2

Subclinical atherosclerosis and myocardial dysfunction have been observed in patients with increased arterial stiffness (Fernandes et al., 2008). For example, Kawasaki disease is characteristic of a cytokine storm in children and has been implicated in heightened arterial stiffness 1 month after symptom onset (Oguri et al., 2014), which can persist for years even after symptom restoration of the disease (Cheung et al., 2008) and could account for long-term orthostatic and haemodynamic challenges later in life (Nakamura et al., 2020). Indeed, reports of Kawasaki disease-like symptoms associated with SARS-CoV-2 infection among children (Verdoni et al., 2020) highlight the potential implications of the virally induced inflammation on the vasculature. Similar findings of heightened carotid stiffness have been observed in children with acute rheumatic fever, a persistent disease characterized by heightened oxidative stress and inflammation that can last for years (Chiu-Braga et al., 2006; Çiftel et al., 2014) and be related independently to an increase in aortic stiffness and atherosclerosis (Nakhai-Pour et al., 2007). In the present investigation, the SARS-CoV-2 group had increased carotid artery stiffness (Figure 2a), which increases risk of both cardiovascular events and all-cause mortality, independently of other cardiovascular disease risk factors (van Sloten et al., 2014; Ziemann et al., 2005). Moreover, a decrease in distensibility is an independent predictor of future cardiovascular events (Ziemann et al., 2005). Our present findings of ~27% lower carotid distensibility and ~22% lower carotid compliance among adults with SARS-CoV-2 compared with healthy adults (Figures 2b,c) could worsen underlying cardiovascular event risk. Heightened arterial

stiffness and lower distensibility might, therefore, pose a risk to the cardiovascular health of young adults with SARS-CoV-2, warranting longitudinal analyses to determine whether the decrements to the vasculature are prolonged.

Young's modulus is a critical variable to understand the arterial wall composition and structure as it relates to cardiovascular disease risk (Blankenhorn & Krams, 1989). In the present investigation, the SARS-CoV-2 subjects had a greater Young's modulus compared with the control subjects (Figure 2d). Furthermore, our present findings of a >1 SD in Young's modulus among the SARS-CoV-2 subjects compared with control subjects might represent a $>15\%$ increase in the risk of developing hypertension over the next 3 years, independent of established risk factors for hypertension and baseline blood pressures, if elasticity does not improve (Liao et al., 1999). These alterations in arterial stiffness and structure among young adults with SARS-CoV-2 suggest that these deleterious effects might be placing those with SARS-CoV-2 at greater risk for cardiovascular events, which is a concern, especially among populations susceptible to cardiovascular complications.

4.2 | Carotid diameters and intima-media thickness with SARS-CoV-2

Injury to vessel walls attributable to acute inflammation, monocyte infiltration and macrophage differentiation is generally accepted as an essential component of atherogenesis (Ross, 1999) and increased cardiovascular mortality rate (Epstein et al., 2000; Espinola-Klein et al., 2002). Arterial remodelling encompasses structural properties that can change over time in response to atherogenic or adverse haemodynamic alterations within the arterial environment, which often manifests in enlarged carotid diameters (Ward et al., 2000). In the present investigation, it is interesting to note the common carotid diameter was statistically greater among young adults with SARS-CoV-2 only during systole compared with healthy controls (Table 2). Whether these alterations persist in the long term remains unknown. However, chronically larger carotid diameters attributable to either atherosclerosis or pressure-related media thickening are associated with greater incidence of stroke, cardiovascular disease and mortality (Sedaghat et al., 2018), which should be considered among those with incessant complications from SARS-CoV-2.

Furthermore, cIMT is an index and independent predictor of future atherosclerosis. Vessel wall inflammation precedes morphological changes caused by inflammatory diseases, as evidenced by heightened cIMT in cross-sectional comparisons of children with acute diagnosis of Kawasaki disease (Wu et al., 2014), Mediterranean fever (Bilginer et al., 2008) or acute rheumatic fever (Çiftel et al., 2014) and in adults with Takayasu disease (Seth et al., 2006) or Behçet's disease (Alan et al., 2004), suggesting that cIMT might change acutely among individuals experiencing heightened infection-related inflammation. However, results from these investigations suggest the acute manifestation of changes in cIMT to be indicative of endothelial dysfunction and inflammation of the vascular wall rather than inherent

fibrotic changes and increased atherosclerotic risk. Furthermore, some studies have suggested an association between *C. pneumoniae*, *H. pylori*, cytomegalovirus or herpes simplex virus infection and carotid atherosclerosis (Espinola-Klein et al., 2000; Melnick et al., 1993; Prager et al., 2002), whereas others have not yielded conclusive associations between infection and cIMT (Hirashima et al., 2002; Maeda et al., 2002). Variations in virulence and invasiveness of infection might be responsible for equivocal findings among a variety of disease states and those with various symptom severity. Given the mild cases of SARS-CoV-2 in the present investigation, it should not be too surprising that cIMT was unaltered by acute SARS-CoV-2 infection in young adults (Table 2). However, persistent symptoms over the course of months might influence cIMT and will be of interest in the future.

4.3 | Carotid pulse wave analysis with SARS-CoV-2

Aortic Alx is a multifaceted marker of ventricular-vasculature coupling typically measured from wave reflections (Laurent et al., 2006). Moreover, cross-sectional analyses of children with Kawasaki disease have revealed several accounts of vascular inflammation, including subclinical arterial stiffness (Oguri et al., 2014) and heightened radial artery Alx (Zheng et al., 2019). Although these short-term manifestations can relate to increased risk of atherosclerotic progression (McCordle et al., 2007; Tobayama et al., 2013), vascular impairments can persist for years after symptom amelioration of diseases associated with vascular inflammation (Pinto et al., 2013, 2017), including long-term changes to arterial stiffness and Alx (Tobayama et al., 2013). The greater aortic Alx and Alx@HR75 among adults with SARS-CoV-2 in the present study (Figure 3), although arguably indicative of the viscoelastic properties of the aorta and large arteries, might therefore be corroborating our previous accounts of arterial stiffness, as evidenced by greater carotid-femoral pulse wave velocity, among young adults who recently contracted SARS-CoV-2 (Ratchford et al., 2020). Additionally, several studies have reported a rise in Alx with age (Fantin et al., 2007; McEniery et al., 2005), and Alx might ultimately be a sensitive index of aortic stiffness in younger adults ≤ 60 years old (Namasivayam et al., 2010). Our present results from young healthy adults are similar to previously reported data from ~ 20 -year-old adults, whereas our Alx data from ~ 20 -year-old adults with SARS-CoV-2 might be more reflective of adults 10 years older (Wojciechowska et al., 2006). Although this cross-sectional analysis does not indicate an irreversible effect of these aortic alterations, more work is needed to track young adults with SARS-CoV-2 longitudinally to determine whether these effects are long lasting.

4.4 | Indices of myocardial oxygen demand and perfusion with SARS-CoV-2

Using morphological analyses of the central arterial pressure wave recorded by tonometry, PWA can also provide a non-invasive index of cardiac ischaemia risk using the Buckberg SEVR index

(Buckberg et al., 1972; Hoffman & Buckberg, 1978). The SPTI, also known as the tension–time integral, is often a surrogate for myocardial oxygen demand. In the present investigation, we observed greater SPTI among young adults who recently contracted SARS-CoV-2, which might be indicative of a mild hypermetabolic (Yu et al., 2020) or hyperdynamic myocardium (Mahjoub et al., 2021), previously observed among those critically ill with SARS-CoV-2. Despite a potential for an acute myocardial stress response among young adults with SARS-CoV-2, the Buckberg SEVR index, a diastolic to systolic pressure–time integral ratio and an index of myocardial oxygen supply (DPTI) to demand (SPTI), appears similar between our SARS-CoV-2 and control groups (Table 3). Although the myocardium might be undergoing a stress response owing to this novel infection, the oxygen supply might, therefore, be maintained. Although these are indirect measures of cardiac oxygen supply and demand, they might provide evidence of a systemic cardiovascular stress response caused by SARS-CoV-2. However, more work is certainly warranted to assess more direct measures of cardiac abnormalities caused by SARS-CoV-2 in young adults.

Ejection duration is an indicator of arterial stiffness, because increases in arterial stiffness result in a shorter ejection duration period (Böcskei et al., 2019). An elevated resting heart rate is also associated with a decrease in ejection duration (Pieringer et al., 2014; Wilkinson et al., 2000) and an increased risk for cardiovascular disease among patients with hypertension, in addition to the general population (Diaz et al., 2005; Dyer et al., 1980). Combined, this evidence of increased arterial stiffening and chronic ejection into stiffer arteries might induce cardiac hypertrophy, even at similar arterial pressures, and might even alter the manner in which the heart is perfused (Lartaud-Idjouadiene et al., 1999). The shorter ejection duration observed in young adults recovering from SARS-CoV-2 (Table 3), therefore, provides additional evidence for increased arterial stiffness that might exacerbate underlying cardiovascular event risk.

4.5 | Study limitations

Although common among studies investigating physiological function in acute infectious diseases, we acknowledge the limitations of a cross-sectional comparison such as this and recognize that some of the underlying group differences might be inherent to inter-subject variability along with continued mild symptoms at the time of testing. The nature of this investigation was not appropriately powered to evaluate sex-specific effects caused by SARS-CoV-2. Furthermore, previous findings suggest little evidence for a sex-based difference in vascular alterations attributable to SARS-CoV-2 (Ratchford et al., 2020). Although the menstrual cycle of the female subject population was not controlled for and variations in contraceptive use between female subjects were observed, contraceptive use and menstrual cycle fluctuations among young healthy females have not been observed to influence carotid distensibility or PWA

(Priest et al., 2018; Wilkinson et al., 1998; Willekes et al., 1999). Additional studies have also suggested no impacts of menstrual cycle or type of contraceptive on central arterial stiffness (Priest et al., 2018). Although future studies should certainly differentiate severity of symptoms and asymptomatic individuals among various age groups, our present results with only one asymptomatic individual failed to show any significant difference between symptomatic and asymptomatic cases of SARS-CoV-2. Longitudinal studies are certainly needed to understand fully the implications of SARS-CoV-2 on arterial health and the potential recovery from this disease. However, the initial results indicating increased arterial stiffness are clinically relevant and warrant attention.

4.6 | Conclusion

Initial evidence suggests an increase in carotid stiffness and aortic augmentation in young adults with SARS-CoV-2. These alterations to the vasculature are clinically relevant because they indicate unfavourable vascular remodelling, mild vascular ageing and potential exacerbation of underlying cardiovascular event risk. Future longitudinal studies with a larger, cardiovascular compromised cohort are warranted to determine whether the observed diminution to cardiovascular health is long lasting among susceptible groups.

ACKNOWLEDGEMENTS

We would like to thank Rebecca Kappus for sharing her equipment and technical knowledge with us, without which this study could not have happened. This study was partially supported by an internal COVID-19 Research Cluster Award at Appalachian State University.

AUTHOR CONTRIBUTIONS

J.L.S., A.S.L. and S.M.R. conceived and designed the research. V.M.P., N.L.S., M.A.A., L.K.K., J.L.S., A.S.L.S. and S.M.R. performed the experiments. All authors analysed the data and interpreted the results of experiments. R.E.S. and S.M.R. prepared the figures. R.E.S., J.L.S., A.S.L.S. and S.M.R. drafted the manuscript. All authors edited and revised manuscript, approved the final version of the 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.

COMPETING INTERESTS

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available upon request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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How to cite this article: Szeghy, R. E., Province, V. M., Stute, N. L., Augenreich, M. A., Koontz, L. K., Stickford, J. L., Stickford, A. S. L., & Ratchford, S. M. (2022). Carotid stiffness, intima-media thickness and aortic augmentation index among adults with SARS-CoV-2. *Experimental Physiology*, 107, 694–707. <https://doi.org/10.1113/EP089481>