Carotid and Femoral Arterial Wall Distensibility During Long-Duration Spaceflight

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INTRODUCTION: This study aimed to assess changes in common carotid (CA) and superficial femoral (FA) arterial stiffness during long-duration spaceflight.

METHODS: Ultrasound imaging was used to investigate the CA and FA of 10 astronauts preflight (PRE), on flight day 15 (FD15), after 4–5 mo (FD4–5m), and 4 d after return to Earth (R+4). Arterial wall properties were assessed through the calculation of strain, stiffness (β), pressure-strain elastic modulus (Ep), and distensibility (DI). Stiffness indices were assessed for potential correlations to measurements of intima-media thickness (IMT).

RESULTS: Significant effects of spaceflight were found for all CA stiffness indices, indicating an increase in arterial stiffness. CA strain was reduced by 34 ± 31% on FD15 and 50 ± 16% on FD4–5m and remained reduced by 42 ± 14% on R+4 with respect to PRE values. On FD4–5m, with respect to PRE values, DI was reduced by 46 ± 25% and β and Ep were increased by 124 ± 95% and 118 ± 92%, respectively. FA arterial stiffness indices appeared to show similar changes; however, a main effect of spaceflight was only found for strain. Correlation analysis showed weak but significant relationships between measurements of CA IMT and arterial stiffness indices, but no relationships were found for FA measurements.

DISCUSSION: The observed change in CA and FA stiffness indices suggest that spaceflight results in an increase in arterial stiffness. That these changes were not strongly related to measurements of IMT suggests the possibility of different mechanisms contributing to the observed results.

KEYWORDS: carotid, femoral, spaceflight, distensibility, arterial stiffness, ultrasound.

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Long-duration spaceflight is known to result in physiological adaptations in part due to a redistribution of fluid throughout the body. Fluid shifts toward the heart result in a loss of plasma volume without changes in cardiac function.[1,15] However, the pooling of blood at the cephalic level[4] is suspected to cause an increase in intracranial pressure and result in visual impairments.[32] Recently, an increase in carotid artery stiffness was reported after long-duration spaceflight,[18] indicating that vascular structural remodeling may occur during spaceflight.

Previous work has shown a reduction in pulse wave transit time after 1 mo of spaceflight,[5] suggesting that changes in vascular properties may occur early during the flight. In a recent publication, our group reported an increase in both common carotid (CA) and superficial femoral artery (FA) intima-media thickness (IMT) after 15 d of spaceflight that persisted for the duration of the flight and 4 d after returning to Earth.[3] This result supports the hypothesis that vascular adaptations occur early during spaceflight and contribute to changes seen postflight; however, to date, no studies have investigated whether the observed changes in IMT are related to changes in vascular stiffness during long-duration spaceflight.

The purpose of the current study was to determine potential changes in CA and FA vascular stiffness during and after long-duration spaceflight. Additionally, as data were collected as a part of our previous IMT study,[3] the secondary purpose of the study was to determine if potential changes in vascular stiffness with spaceflight were related to the observed increases in IMT. It was hypothesized that long-duration spaceflight would result in increased arterial stiffness, which would be associated with changes in IMT.

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METHODS

Subjects

Ultrasound imaging data were collected from 10 astronauts (7 men, 3 women; 47 ± 5 yr of age; weight 69 ± 12 kg; height: 172 ± 8 cm) who participated in the Vessel Imaging Study. Before participation, astronauts were informed of all study protocols and procedures and provided informed consent for participation. Both the National Aeronautics and Space Administration (NASA) and European Space Agency (ESA) ethics committees provided approval for all protocols and procedures used in the study (IRB pro 0340). During the spaceflight missions, each astronaut received standardized meals and were required to perform daily physical activity. However, food and fluid intake and exercise duration and intensity were not strictly controlled and differed between participants.

Equipment

Echo Doppler ultrasound was used to acquired images of the CA and FA (Vivid Q, GE Healthcare, Chicago, IL). All imaging was conducted using a 7.5-MHz linear probe. In-flight blood pressure was measured using Cardiopres (CDL CBPD) developed by CNES with TNO-TPD-Biomedical Instrumentation (BMI, Eindhoven, The Netherlands). Pre- and postflight blood pressure was performed using the Portapres Model 3.1 developed by TNO-TPD-BMI.

Procedures

Astronauts received 3 h of ultrasound training before the mission and performed their own ultrasound imaging throughout the study. During the examinations, a trained sonographer provided guidance to the astronaut regarding proper probe placement and orientation to ensure that the vessel of interest was adequately imaged. For the examinations, astronauts were instructed to first hold the ultrasound probe in a transverse (horizontal) position, to provide a cross-sectional image of the artery. In this orientation, the artery appears as a black circle, which was easily identifiable for the astronauts. For the CA, the probe was located at the bottom of the neck in contact with the clavicle, and for the FA, the probe was positioned on the upper third portion of the thigh, just below the femoral bifurcation. In each position, the probe was held stationary for approximately 10 s while video was recorded. All ultrasound video collected during spaceflight was downlinked to the ground control center [CADMOS, French National Space Agency (CNES), Toulouse, France] in near real time.

Ultrasound images of the CA and FA were recorded preflight (PRE) in the supine position, during flight, and 4 d after return to Earth (R+4), also in the supine position. All ultrasound imaging was conducted a minimum of 2 h after a meal and 24 h after any sustained moderate- to high-intensity physical activity. In-flight ultrasound video was collected on day 15 of the spaceflight (FD15) and 15 d before returning to Earth. Due to the different spaceflight durations, the later flight measurement occurred between 115 and 165 d of spaceflight, with some astronauts conducting an additional examination on day 135 of flight. For analysis purposes, late duration flight values were considered to be the average of measurements obtained between 115 and 165 d of spaceflight (FD4–5m).

Recorded videos were reviewed frame by frame using VirtualDub software (www.virtualdub.org). Frames of maximum (systolic) and minimum (diastolic) diameter were determined and manual caliper measurements were made. Diameter measurements for 5–8 cardiac cycles were averaged to provide a single systolic and diastolic measurement for each imaging session. Vessel strain was then calculated as Strain = (Ds − Dd)/Dd where Ds is the systolic diameter and Dd is the diastolic diameter.[17]

Three additional indices of vascular stiffness were calculated for PRE, FD4–5m, and R+4 using measurements of arterial systolic and diastolic blood pressure. Brachial arterial blood pressure measurements were made on the same day as the ultrasound assessments (PRE, FD4–5m, and R+4). Three indices of arterial stiffness were calculated for the elastic modulus [Ep = (Ps − Pd)/Strain], stiffness index [β = ln(Ps/Pd)/Strain], and arterial distensibility [DI = Strain/(Ps − Pd)], where Ps is systolic blood pressure, Pd is diastolic blood pressure, and Strain is calculated as indicated above from vessel diameter measurements.[17,20] Ratios between calculated CA and FA stiffness indices were calculated to determine potential regional differences in response.

Statistical Analysis

The effects of spaceflight on Strain, Ep, β, and DI were assessed using a one-way repeated measures ANOVA (SigmaPlot 12.5, Systat Software Inc., Chicago IL). Before proceeding with the ANOVA, data sets were tested for both normality (Shapiro-Wilk) and equal variance. In the case of significant main effects, Tukey post hoc testing was used to assess all pairwise comparisons. Pearson correlation analysis was used to determine potential relationships between arterial stiffness indices and IMT measurements for PRE, FD4–5m, and R+4. For all tests, significance was set at $P < 0.05$.

RESULTS

Ultrasound videos during spaceflight were successfully obtained from 8 of the 10 astronauts (6 men, 2 women) with an equipment failure preventing several in-flight data acquisition sessions for 2 of the astronauts. As in-flight data were not available for these astronauts, they were excluded from the analysis. Additionally, a third astronaut (male) was excluded from the FA analysis due to the recorded in-flight images being of insufficient quality for measurements.

Systolic and diastolic arterial pressure measurements are presented in **Table I**. There was a significant effect of spaceflight on diastolic blood pressure [$F(2,7) = 5.275$, $P = 0.02$], with a difference being found between R+4 and FD4–5m. Conversely, systolic blood pressure was not different with spaceflight [$F(2,7) = 0.472$, $P = 0.633$]. CA and FA IMT measurements

Table I. Measurements of Systolic and Diastolic Arterial Blood Pressure and Common Carotid Artery and Superficial Femoral Artery Intima-Media Thickness.

	PRE	FD15	FD4–5m	R+4
Systolic BP (mmHg)	119.1 ± 9.9	–	115.1 ± 10.1	116.3 ± 8.4
Diastolic BP (mmHg)	68.4 ± 7.0	–	66.6 ± 6.4†	76.3 ± 7.0
CA IMT (mm)	0.60 ± 0.05	0.66 ± 0.06*	0.67 ± 0.04*	0.64 ± 0.06*
FA IMT (mm)	0.56 ± 0.09	0.62 ± 0.11*	0.64 ± 0.10*	0.58 ± 0.10

BP: blood pressure; CA: common carotid artery; IMT: intima-media thickness; FA: superficial femoral artery.
Values (mean ± SD) show the measurements of systolic and diastolic arterial blood pressure and CA (N = 8) and FA (N = 7) IMT before flight (PRE), 15 d into the flight (FD15), late in the flight (FD4–5m), and 4 d after returning to Earth (R+4). Values statistically different from PRE are denoted by *. For diastolic blood pressure, † indicates differences from R+4. IMT Data were originally published in Arbeille et al.[3] and are reprinted with permission.

also showed significant changes with spaceflight as previously described[3] and are reproduced in Table I with permission.

Assessment of CA stiffness indices (**Fig. 1**) found a significant effect of spaceflight for all calculated indices [Strain: $F(3,7) = 9.61$, $P < 0.001$; β: $F(2,7) = 7.204$, $P = 0.007$; Ep: $F(2,7) = 6.459$, $P = 0.01$; DI: $F(2,7) = 10.093$, $P = 0.002$]. Compared to PRE values, CA strain (Fig. 1A) was reduced on FD15 and remained lower on FD4–5m and R+4. CA β (Fig. 1B) and CA Ep (Fig. 1C) were increased and CA DI was decreased compared to PRE on FD4–5m, but returned to PRE levels on R+4. For all calculated stiffness indices, significant relationships to IMT measurements were found (**Table II**).

Assessment of FA Strain (**Fig. 2A**) showed a significant effect of spaceflight [$F(3,6) = 3.193$, $P = 0.049$]; however, post hoc testing did not find a difference from PRE values on FD4–5m ($P = 0.054$), or R+4 ($P = 0.096$). Although mean values appeared to be different and show changes similar to those found with the CA, no effects of spaceflight were found for FA β [**Fig. 2B**, $F(2,6) = 2.951$, $P = 0.091$], FA Ep [**Fig. 2C**, $F(2,6) = 3.092$, $P = 0.083$], or FA DI [**Fig. 2D**, $F(2,6) = 1.21$, $P = 0.332$]. No significant relationships were found between calculated FA stiffness indices and IMT measurements (Table II). Additionally, the ratio between CA and FA vascular stiffness was not different with spaceflight for any of the calculated indices [**Table III**; Strain: $F(3,6) = 0.162$, $P = 0.921$; β: $F(3,6) = 0.219$, $P = 0.882$; Ep: $F(3,6) = 0.219$, $P = 0.882$; DI: $F(3,6) = 0.162$, $P = 0.921$].

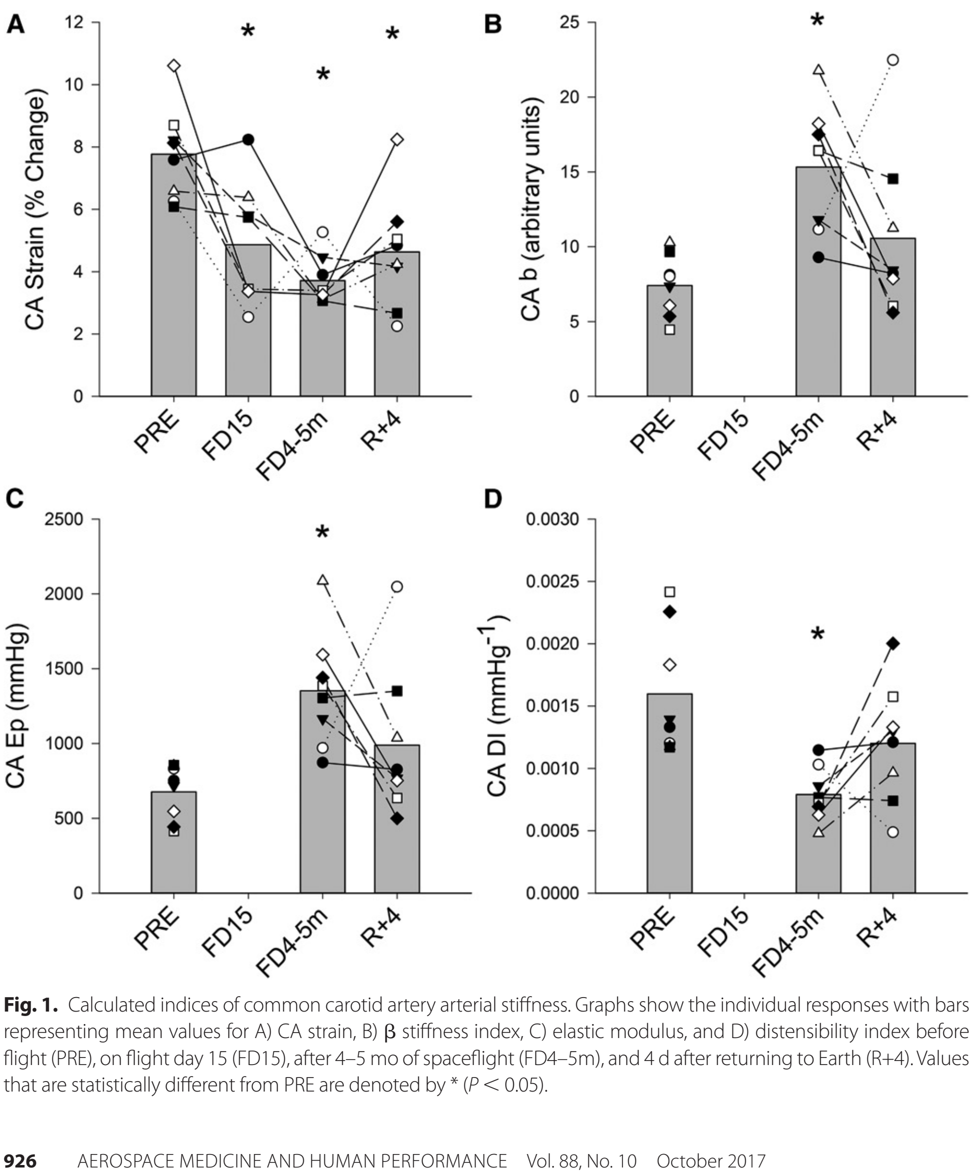

Fig. 1. Calculated indices of common carotid artery arterial stiffness. Graphs show the individual responses with bars representing mean values for A) CA strain, B) β stiffness index, C) elastic modulus, and D) distensibility index before flight (PRE), on flight day 15 (FD15), after 4–5 mo of spaceflight (FD4–5m), and 4 d after returning to Earth (R+4). Values that are statistically different from PRE are denoted by * ($P < 0.05$).

DISCUSSION

Exposure to microgravity is known to result in cardiovascular changes. However, the exact nature, magnitude, and mechanisms responsible are still being investigated. Recently, a reduction in carotid artery distensibility has been reported after long-duration spaceflight.[18] Therefore, the purpose of the present study was to determine if vascular stiffness is altered during long-duration spaceflight and if stiffness indices relate to measurements of arterial IMT. Results indicate increased CA stiffness during spaceflight with moderate relationships to measurements of CA IMT. Similar to the CA, FA strain also showed a decrease with spaceflight; however, in contrast, changes with spaceflight for any of the other FA stiffness indices did not reach statistical significance and values were not related to measurements of FA IMT.

Cephalad fluid shifts have often been implicated as a mechanism for observed cardiovascular changes with microgravity exposure. Due to the removal of the hydrostatic pressure gradient

Table II. Pearson Correlation Analysis of Measurements of Common Carotid Artery (CA) and Superficial Femoral Artery (FA) IMT and Calculated Stiffness Indices.

VESSEL & RELATIONSHIP	r	*P*
CA		
Strain vs. IMT	−0.388	0.061
β vs. IMT	0.472	0.020
Ep vs. IMT	0.506	0.012
DI vs. IMT	−0.567	0.004
FA		
Strain vs. IMT	−0.141	0.542
β vs. IMT	0.198	0.389
Ep vs. IMT	0.206	0.369
DI vs. IMT	−0.123	0.594

CA: common carotid artery; IMT: intima-media thickness; β: stiffness; Ep: elastic modulus; DI: distensibility index; FA: superficial femoral artery.
Values show the results of the correlation analysis between measurement of CA [r(24)] and FA [r(21)] IMT and calculated stiffness indices from PRE, FD4–5m, and R+4.

in microgravity and the redistribution of fluid, arterial pressure would be expected to be increased at the carotid level and decreased at the level of the femoral artery. Increased arterial pressure or pulse pressure has been found to be associated with increased arterial stiffness;[28,30] therefore, increases in CA stiffness would have been expected with no change or even reductions at the level of the FA. This appeared to be the case as only indices of CA stiffness showed an effect of spaceflight. However, there were strong trends for FA results to mimic those of the CA and a lack of change in the ratio between CA stiffness indices and FA indices indicates that large regional differences did not exist between the two sites. It would then follow that changes in arterial pressure due to cephalad fluid shift may not be a major contributing factor in the observed changes in arterial stiffness.

Chronic alterations in vascular stiffness ultimately involve cellular processes influenced by both mechanical and metabolic factors.[33] In general, increases in vascular stiffness result from increased levels of collagen and decreased levels of elastin within the vascular wall.[31,33] Results from the current study suggest that vascular structural remodeling may not be the primary mechanism in the observed increase in arterial stiffness as change during spaceflight tended to return to PRE values only 4 d after returning to Earth. Additionally, in our study, changes in vessel strain consistent with increased vascular stiffness were also seen after only 15 d of spaceflight. This is similar to results from another spaceflight experiment that reported reduced total arterial compliance, calculated as cardiac stroke volume divided by arterial blood pressure, after 5 to 18 d of spaceflight.[26] Together, these results suggest the possibility of a secondary mechanism that contributes to changes in vascular properties with only short durations of microgravity exposure.

Alterations in physical activity with spaceflight may also have contributed to changes in arterial properties. On average, astronauts only performed 30 min of vigorous activity each day. This is similar to individuals with sedentary lifestyles on Earth which could contribute to metabolic dysregulation and vascular remodelling.[6,18] However, in the present study, physical activity and nutrition were not strictly controlled between astronauts, making it difficult to discern links between these variables and changes in vascular properties.

Recently, insulin resistance and hyperglycemia have been reported in astronauts after 6 mo aboard the International Space Station (ISS),[18] suggesting the possibility of metabolic dysfunction contributing to changes in vascular mechanical properties.[29,33] Studies have suggested that insulin resistance and chronic elevations of blood glucose could be associated with the formation of advanced glycation end products, which could lead to increased oxidative stress and vascular damage.[7] Results from the MARS 500 confinement study, which found similar changes in IMT measurements,[2] also reported increased oxidative stress markers.[9,24] Therefore, changes in metabolic function with spaceflight, either due to the microgravity environment or long durations in confined spaces, may contribute to the observed increase in stiffness.

Of additional consideration is the potential influence of psychological stress on vascular properties. Spaceflight is a high risk situation where astronauts are confined in close proximity to a limited number of crewmembers for the duration of the mission, which could result in a high level of psychological stress.[10,13] A study has shown acute effects of laughter and stress on arterial stiffness where stress resulted in an increase in pulse wave velocity, suggesting increased arterial stiffness.[27] Thus, it may be possible that environmental stress, independent of the effects of microgravity, is a contributing factor to changes in vascular structure with long-duration spaceflight.

The current study hypothesized that indices of arterial stiffness would be related to measurements of IMT. This hypothesis was in part supported by weak, but significant relationships between indices of CA stiffness and IMT measurements, but no relationships were found between measurements of FA IMT and stiffness indices. Although it was hypothesized that the observed changes in IMT would be related to vascular stiffness, studies have suggested the independent nature of these variables. In children with adenotonsillar hypertrophy, an increase in CA IMT has been observed with no changes in vessel stiffness.[11] Similarly, a separate study reported increased IMT associated with increased arterial compliance[30] and, in a study of 524 young adults, no relationship was found between a measure of arterial stiffness and IMT.[21] While the relationships between CA stiffness and IMT suggest that changes in IMT are indicative of vascular remodeling leading to changes in vascular stiffness, the weakness of this relationship and the lack of association with FA measurements suggest the possibility that IMT and vascular stiffness are independent. It should also be noted that the ultrasound measurements of IMT used for the current study did not allow for the differentiation of IMT alterations due to vascular structure or active vascular tone. Therefore, different mechanisms could be contributing to the observed changes in IMT and vascular stiffness with spaceflight.

The observed increases in stiffness and in IMT suggest potential increased cardiovascular risk. Increased central arterial stiffening and IMT are hallmarks of the aging process and the consequence of many disease states such as diabetes, atherosclerosis, and chronic renal disease.[12,23,29] Increased IMT is

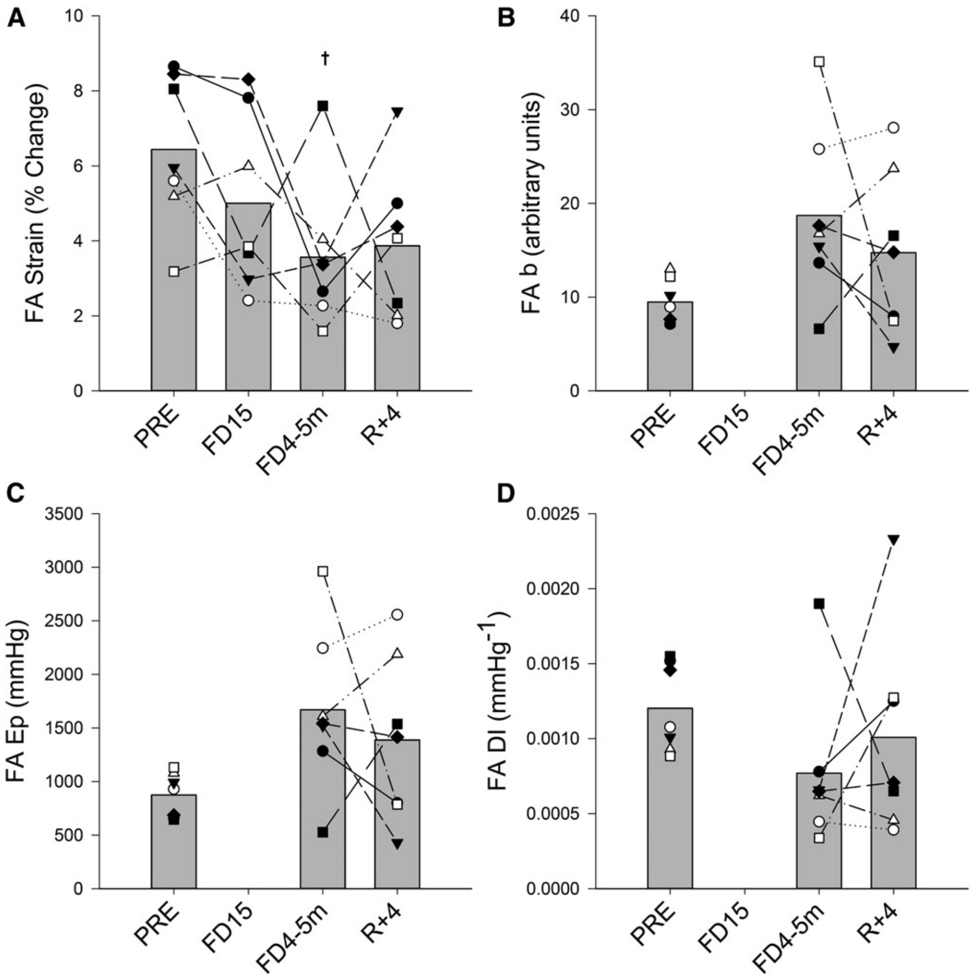

Fig. 2. Calculated indices of superficial femoral artery arterial stiffness. Graphs show the individual responses with bars representing mean values for A) FA strain, B) β stiffness index, C) elastic modulus, and D) distensibility index before flight (PRE), on flight day 15 (FD15), after 4–5 mo of spaceflight (FD4–5m), and 4 d after returning to Earth (R+4). $^{\dagger}P = 0.056$.

commonly considered a cardiovascular risk factor as it has been associated with the development of a greater number of cardiovascular events.[8,22] With respect to aging, the observed changes in stiffness and IMT with spaceflight correspond to changes expected with approximately 20 yr for healthy subjects on Earth.[16,19,25] Therefore, it could be suggested that microgravity exposure accelerates the effects of aging or promotes vascular pathological processes.

Indices of vascular stiffness appeared to return to PRE levels 4 d after returning to Earth. As Hughson et al.[18] reported increased vascular stiffness 22–38 h after long-duration spaceflight, the results of the current study suggest a rapid recovery post-spaceflight. This may indicate that the observed changes in vascular stiffness are functional rather than structural in nature and may not be directly related to the development of cardiovascular disease. However, it should also be noted that a study of 128 patients with moderate to significant carotid stenosis[14] did not find a correlation between arterial wall thickness and the degree of stenosis or plaque volume, suggesting that remodeling of the arterial wall is not necessarily a requirement for the development of atheromatous disease. Therefore, these results highlight that the potential risk associated with increased vascular stiffness and IMT during spaceflight, even if reversible in a healthy population upon return to Earth, is deserving of further study in the preparation for longer duration spaceflight.

The current study used ultrasound measurements of CA and FA arterial diameter and brachial arterial blood pressure measurements for the determination of arterial stiffness. Accurate measurements of arterial stiffness require the simultaneous measurement of arterial pressure and vessel dimensions at the same location in the vascular tree. As this was not the case in the current study, indices of vascular stiffness parameters were presented which could be influenced by differences in arterial pressure at the location of the CA and FA or by normal variations in arterial pressure between time of ultrasound assessment and blood pressure measurement.

The influence of arterial pressure measurements on vascular stiffness indices may be particularly evident for the assessments post-spaceflight. While results from the current study indicated a rapid recovery of arterial stiffness upon return to Earth, this was mainly due to arterial pressure measures. In contrast to stiffness indices calculated with arterial blood pressure measurements, arterial strain, calculated from measurements of arterial systolic and diastolic diameter, was significantly reduced post-spaceflight, indicating a smaller change in diameter within a cardiac cycle, potentially due to increased arterial stiffness. During flight, changes in arterial strain and the calculated stiffness indices both indicate increased arterial stiffness. However, the mismatch between strain and the stiffness indices postflight raises questions with respect to the recovery of arterial properties upon return to Earth. Studies are currently in progress to further investigate spaceflight recovery responses with simultaneous pressure and diameter assessments being planned up to 1 yr postflight.

The sample size in the current experiment was also a limiting factor, which, in part due to individual variability in responses, may have contributed to the lack of significant results for some variables and prevented testing for potential sex differences in responses. Where carotid artery responses were very consistent between participants leading to significant findings, statistical power for the assessment of FA responses ($N = 7$) was very low. In addition, as the FA is anatomically further

Table III. Ratio Between Calculations of CA and FA Stiffness Indices.

	PRE	FD15	FD4–5m	R+1
Strain	1.34 ± 0.65	1.14 ± 0.49	1.34 ± 0.70	1.31 ± 0.53
β	0.86 ± 0.31	–	1.02 ± 0.71	0.90 ± 0.44
Ep	0.86 ± 0.31	–	1.02 ± 0.71	0.90 ± 0.44
DI	1.34 ± 0.65	–	1.34 ± 0.70	1.31 ± 0.53

CA: common carotid artery; FA: superficial femoral artery; β: stiffness; Ep: elastic modulus; DI: distensibility index; PRE: before flight; FD15: flight day 15; FD4–5m: 4–5 mo into the flight; R+1: 1 d after return to Earth.
Values (mean ± SD) show the ratio between CA and FA for each of the calculated stiffness indies at each measurement time point.

from the surface than the CA, the resolution of the FA images is generally of lower quality, which may have contributed to less accurate measurements of FA systolic and diastolic diameter. Future studies using ultrasound measurements during spaceflight will look to use radiofrequency signal to provide better measurements of vessel diameters. We believe that future results will support the finding of this paper of increased vascular stiffness of both the FA and CA with spaceflight.

In the current study, many factors that could contribute to changes in vascular structure and function were not controlled such as physical activity, food and water intake, and mental stress. Therefore, in this discussion, several potential mechanisms of vascular change were presented. In the future, a more accurate evaluation of these variables will be needed to better understand vascular changes with spaceflight and develop effective countermeasures to maintain astronaut health.

Results of the current study showed increased carotid arterial stiffness with long-duration spaceflight. Femoral artery assessments suggested similar increases in stiffness; however, results did not reach statistical significance due to a large degree of individual variability and a small sample size. Measures of CA IMT were weakly correlated to CA stiffness indices while no relationships were found for measurements of FA IMT and FA stiffness indices. The weak correlation and lack of relationship between measures of IMT and arterial stiffness indices suggest the possibility of different mechanisms involved with these responses. The observed changes in vascular stiffness with long-duration spaceflight suggest the need for future studies to determine the mechanism involved and to develop effective countermeasures for longer duration spaceflights.

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