The influence of habitual endurance exercise on carotid artery strain and strain rate in young and middle-aged men

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Edited by: Gail Thomas

Abstract
Central arterial stiffness is an independent predictor of cardiovascular risk that can be modified by exercise training. However, conventional local measures of carotid artery stiffness display conflicting responses to habitual endurance exercise in young and older adults. Two-dimensional (2D)-Strain imaging of the common carotid artery (CCA) quantifies circumferential deformation (strain) of the arterial wall across the cardiac cycle, which is more sensitive at detecting age-related alterations in CCA stiffness than conventional methods. Therefore, the study was designed to examine the relationship between habitual endurance exercise (running) and CCA 2D-Strain parameters in young and middle-aged men. Short-axis ultrasound images of the CCA were obtained from 13 young non-runners [23 years of age (95% confidence interval: 21, 26 years of age)], 19 young runners [24 (22, 26) years of age], 13 middle-aged non-runners [54 (52, 56) years of age] and 19 middle-aged runners [56 (54, 58) years of age]. Images were analysed for peak circumferential strain (PCS; magnitude of deformation) and systolic and diastolic strain rates (S-SR and D-SR; deformation velocity), and group differences were examined via two-way ANOVA. PCS, S-SR and D-SR were attenuated in middle-aged men compared with young men (all $P \leq 0.001$). PCS and S-SR were elevated in young and middle-aged runners when compared with non-runners ($P = 0.002$ and $P = 0.009$, respectively), but no age $\times$ training status interaction was observed. In contrast, there was no influence of habitual running on D-SR. Habitual exercise is associated with comparable improvements in CCA 2D-Strain parameters in young and middle-aged men, but the age-related decline in PCS and S-SR might be more amenable to habitual endurance exercise than D-SR.

KEYWORDS
ageing, carotid artery, exercise, strain
INTRODUCTION

Arteriosclerosis, a hallmark of advanced ageing, is characterized by alterations to the elastic composition of the arterial wall matrix of large central arteries, which promote arterial stiffening (Lakatta & Levy, 2003) and impair the ability of vessels to buffer pulsatile blood flow during systole (Liao et al., 1999). Consequently, increased aortic and common carotid artery (CCA) stiffness are both associated with elevated blood pressure (Kaesel et al., 2012; Liao et al., 1999), impaired cardiac function (Bruno et al., 2017; Kawaguchi, Hay, Fetics, & Kass, 2003) and microvascular damage of target organs (O’Rourke & Safar, 2005; van Sloten & Stehouwer, 2016) and are independent predictors of cardiovascular disease and all-cause mortality (Laurent et al., 2006; van Sloten et al., 2014). Therefore, management strategies capable of attenuating the age-related progression of aortic and CCA stiffening have considerable clinical implications.

Regular endurance exercise can attenuate both aortic and CCA stiffening in middle-aged and older healthy individuals (Tanaka & Safar, 2005; Tanaka et al., 2000; Vaitkevicius et al., 1993), and cardiorespiratory fitness (CRF) is inversely associated with aortic and CCA stiffness in ageing populations (Tanaka, DeSouza, & Seals, 1998; Vaitkevicius et al., 1993). However, the influence of CRF (Ferreira et al., 2005; Ferreira, Twisk, Stehouwer, van Mechelen, & Kemper, 2003; Tanaka et al., 2000) and exercise training (Heydari, Boutcher, & Boutcher, 2013; Kakiyama et al., 2005; Montero, Breenfeldt-Andersen, Oberholzer, & Haider, 2017; Tanaka et al., 2000) on aortic and CCA stiffness appears to be less consistent in young, asymptomatic individuals, leading some to propose that only aged arteries can be modulated by exercise (Montero et al., 2017).

The majority of these studies used aortic pulse wave velocity (aPWV) as the ‘gold-standard’ non-invasive measurement of ‘central’ arterial stiffness. Although aPWV is a valuable marker of central artery stiffness and an independent predictor of cardiovascular risk (Laurent et al., 2006), it is limited to the aorta and assumes vascular homogeneity. This is problematic, because adults with similar aPWV can demonstrate differences in local indices of CCA stiffness (Priest, Shenouda, & MacDonald, 2018), implying that arteriosclerosis has a heterogeneous effect at distinct regions of the central arterial tree. Given that the CCA is a frequent site of atheroma formation (Laurent et al., 2006), local measures of CCA stiffness provide important prognostic information beyond aPWV and are independently associated with incident stroke (van Sloten et al., 2015). Accordingly, sensitive measures of local CCA stiffness are required alongside aPWV to characterize arterial stiffness comprehensively across the arterial tree. Although conventional CCA stiffness indices, such as $\beta$-stiffness index ($\beta$-stiffness), Peterson’s elastic modulus ($E_p$) and distensibility coefficient have valuable reference standards (Engelen et al., 2015; Uejima et al., 2020), these parameters also assume vascular homogeneity, are limited to one-dimensional measurement of lumen distension and display low intra- and inter-observer reliability (Bjällmark et al., 2010). This emphasizes that a sensitive ‘gold-standard’ measure of CCA stiffness does not yet exist and might explain why the influence of exercise training on conventional CCA stiffness parameters is varied in young individuals (Montero et al., 2017; Tanaka et al., 2000) and not always consistent with aPWV responses in older populations (Shibata et al., 2018).

Recently, two-dimensional strain (2D-Strain) imaging has emerged as a valuable technique to detect heterogeneous wall motion of the CCA, which provides localized deformation characteristics of the entire arterial wall (Bjällmark et al., 2010; Pugh et al., 2018; Rosenberg et al., 2018; Yang et al., 2018). This technique quantifies the magnitude and rate of circumferential deformation (strain) of the CCA wall across the cardiac cycle (Bjällmark et al., 2010), which has been reported to offer a more sensitive characterization of age-related increases in CCA stiffness than conventional measures, as well as superior intra- and inter-observer reliability (Bjällmark et al., 2010; Rosenberg et al., 2018). Specifically, peak circumferential strain (PCS) and systolic and diastolic strain rates (S-SR and D-SR) are elevated in young men with high CRF in comparison to those with lower CRF, despite a lack of differences in conventional indices of CCA stiffness or blood pressure (Pugh et al., 2018). Given that PCS is likely to reflect the overall loading capacity of the CCA, whereas S-SR and D-SR relate more to the intrinsic elastic properties of the vessel (Teixeira et al., 2015), it is plausible that the influence of habitual endurance exercise on these distinct CCA stiffness parameters might differ between young and middle-aged individuals. Therefore, 2D-
Strain imaging might provide new insight into the interaction between habitual endurance exercise and healthy ageing of large elastic central arteries. Accordingly, the primary aim of this study was to examine the relationship between habitual endurance exercise and CCA 2D-Strain parameters in young and middle-aged men. We hypothesized that male habitual runners would exhibit elevated 2D-Strain parameters in comparison to age-matched male non-runners and that ageing would attenuate 2D-Strain parameters irrespective of training status.

2 | METHODS

2.1 | Participants

Sixty-four male participants were recruited, including 13 young non-runners [23 [95% confidence interval (CI): 21, 26] years of age] 19 young runners [24 (22, 26) years of age], 13 middle-aged non-runners [54 (52, 56) years of age] and 19 middle-aged runners [56 (54, 58) years of age]. All participants were normotensive non-smokers with no history of cardiovascular, metabolic or renal disease or any contraindications to exercise. None of the participants reported taking prescribed medication, and all middle-aged participants were screened for ECG abnormalities at rest and during exercise (SECA CT8000P; Vogel & Halke, Hamburg, Germany) (Drezner et al., 2013). Middle-aged runners had performed ≥ 25 kilometers week⁻¹ of moderate to intense training for ≥ 10 years, whereas young runners had performed ≥ 50 kilometers week⁻¹ of moderate to intense training for ≥ 2 years. Middle-aged and young male non-runners were recreationally active, i.e. ≤ 3 hours of structured physical activity per week for ≥ 10 and ≥ 2 years, respectively. We specifically chose to recruit middle-aged runners (i.e. 50–60 years) rather than older runners into the study, because this decade appears to represent a focal point during which central arterial stiffness (as determined by aPWV) increases exponentially as part of healthy vascular ageing (AlGhatrif et al., 2013).

In addition, owing to the recognized differences in haemodynamic regulation between men and women (Hart & Charkoudian, 2014), only male participants were recruited into the study. Ethical approval was provided by Cardiff Metropolitan University’s School of Sport and Health Sciences Research Ethics Committee (16/7/02R), and the study conformed to the Declaration of Helsinki (2008) except for registration in a database. All participants were informed of the methods and study design verbally and in writing before providing written informed consent.

2.2 | Experimental procedures

The study implemented a cross-sectional design and was conducted in a quiet, temperature-controlled room. Participants reported to the laboratory on two separate occasions having refrained from strenuous exercise, alcohol intake and caffeine intake for 24 hours before each visit. During visit 1, preliminary screening was conducted, including anthropometric measurements, brachial blood pressure via manual sphygmomanometry and a maximal exercise test on an upright cycle ergometer (Corival; Lode BV, Gronigen, The Netherlands) to obtain peak oxygen uptake ($V_{O2peak}$) as previously described (Wakeham et al., 2019). For visit 2, participants attended the laboratory having fasted for ≥ 6 hours. Participants rested supine for 10 min before aPWV and central blood pressure were assessed. Additionally, short-axis and longitudinal ultrasound images of the right CCA were recorded for post hoc analysis of 2D-Strain parameters and conventional measures of CCA stiffness.

2.3 | Aortic pulse wave velocity

A high-fidelity micromanometer-tipped probe was used to obtain sequential ECG-gated pressure waveforms at the site of maximal arterial pulsation of the carotid and femoral arteries to calculate aPWV in accordance with applanation tonometry guidelines (Van Bortel et al., 2012). Central blood pressure was estimated by applying a validated transfer function (Van Bortel et al., 2012) to radial artery waveforms collected via the same probe (SphygmoCor; AtCor Medical, Sydney, NSW, Australia).

2.4 | Carotid artery ultrasonography and two-dimensional strain imaging

Short-axis grey-scale cine loops of the right CCA were recorded 1–2 cm proximal to the carotid bulb using a commercially available ultrasound system (Vivid Q; GE Medical, Oslo, Norway) and a 12 MHz linear array transducer at a consistent frame rate of 92.3 frames s⁻¹. Longitudinal B-mode images were then obtained at an insonation angle < 60 deg to record CCA diameter and mean blood flow velocity simultaneously. All images were acquired at a constant depth by a single trained sonographer (J.S.T).

2.5 | Ultrasound image analysis

2.5.1 | Two-dimensional strain

Speckle-tracking software quantifies the motion of the arterial wall by automatically identifying speckles in the short-axis ultrasound image, which are subsequently tracked across the cardiac cycle (Catalano, Lamberti-Castronuovo, Catalano, Filocamo, & Zimbudali, 2011). For quantification of strain and strain rates, a region of interest (ROI) was placed manually over the entire CCA wall circumference, ensuring accurate alignment with the lumen–wall interface. Within this ROI, movement of speckles was tracked frame by frame throughout systole and diastole within six evenly distributed segments using a speckle-
tracking algorithm inherent to the software (EchoPac v.112; GE Vingmed Ultrasound, Horten, Norway), which generated strain and strain rate curves. PCS, S-SR and D-SR were measured as ‘global’ values reflecting the averaged values obtained from each ROI segment over three consecutive cardiac cycles and therefore represent the circumferential motion of the entire CCA wall. PCS was identified as the greatest peak in the interpolated circumferential strain curve and represents the magnitude of CCA circumferential deformation from diastole to peak systole. S-SR was identified as the largest positive peak in the strain rate curve that occurred after the QRS complex, and D-SR was determined as the largest negative peak in the strain rate curve after the T-wave of the ECG.

2.5.2 Common carotid arterial blood flow

Analyses of CCA diameter and flow were performed using semi-automated custom-designed edge-detection and wall-tracking software, which is independent of investigator bias and has been described comprehensively elsewhere (Townsend et al., 2015; Woodman et al., 2001). From synchronized diameter and velocity data, blood flow (the product of lumen cross-sectional area and Doppler velocity) was calculated at 30 Hz. Longitudinal B-mode ultrasound images were analysed continuously over 1 min of recording to acquire the average systolic (maximum) and diastolic (minimum) CCA diameter and the mean CCA blood flow. CCA systolic and diastolic diameters were then used to calculate CCA Ep and β-stiffness (Bjällmark et al., 2010; Pugh et al., 2018).

2.6 Statistical analysis

Power analyses of CCA 2D-Strain parameters were conducted a priori by sampling data from two separate studies, one investigating the effect of ageing on 2D-Strain parameters in untrained individuals (Bjällmark et al., 2010) and the other investigating the effect of high CRF on 2D-Strain parameters in young men (Pugh et al., 2018). A mean difference in PCS of 3.8% (Cohen’s d effect size = 4.19) was detected between young and old individuals, whereas a mean difference of 2.3% (d = 0.7) was detected between highly and moderately fit young men. Accordingly, we estimated that a sample of 60 participants within a four-group cross-sectional study design would detect a 2.3% (d = 0.7) difference in PCS with 90% power at a two-sided 0.05 significance level. Statistical analysis was conducted using the SPSS statistical software package (v.23.0; SPSS Inc., Chicago, IL, USA). All data are presented as means and 95% CIs, with statistical significance set to P ≤ 0.05. A two-factor ANOVA was used to determine the main effects of age, training status and whether there was an interaction between these factors (age × training status). When a significant interaction was observed, post hoc comparisons with Bonferroni corrections were conducted to identify significant differences among group mean values. Additionally, analysis of covariance (ANCOVA) was conducted with central mean arterial pressure and CCA diastolic diameter individually set as covariates to control for their potential cofounding influence on 2D-Strain parameters. Finally, linear regression analysis was also conducted to quantify the relationship between CRF (VO2peak), 2D-Strain parameters and aortic stiffness (aPWV) in young and middle-aged men by grouping all the young and middle-aged participants into two separate groups.

3 RESULTS

3.1 Participant characteristics

Peak oxygen uptake was higher in runners compared with non-runners (P ≤ 0.001) and lower with age (P ≤ 0.001; Table 1), but no age × training status interaction was observed. Non-runners had a higher body mass index than runners (P ≤ 0.001), but there were no age-related differences. Runners demonstrated lower resting heart rates than non-runners (P = 0.001), as well as lower brachial systolic and diastolic blood pressure (P = 0.032 and P = 0.003, respectively), whereas diastolic pressure was elevated with age irrespective of training status (P ≤ 0.001). No age × training status interaction was observed for any of these parameters (Table 1).

3.2 Central haemodynamics and aortic pulse wave velocity

Central systolic blood pressure and pulse pressure were higher in middle-aged men compared with young men (both P ≤ 0.001), whereas both central diastolic and mean arterial pressures were lower in runners compared with non-runners (P = 0.018 and P = 0.008, respectively; Table 2). No other main effects of age or training status were observed for central pressures, nor were any age × training status interactions. aPWV was elevated in middle-aged men compared with young men (P ≤ 0.001) and lower in runners than non-runners (P ≤ 0.001). However, no age × training status interaction was observed (Table 2).

3.3 Common carotid artery morphology and conventional stiffness indices

Systolic, diastolic and mean CCA diameters were elevated in middle-aged men compared with young men (P = 0.015, P ≤ 0.001 and P = 0.005, respectively). However, there was no main effect of training status or an age × training status interaction for any of these parameters (Table 2). There were no main effects of age or training status on mean blood flow. CCA distension was lower with age (P ≤ 0.001) and elevated in runners compared with non-runners (P ≤ 0.001), while Ep and β-stiffness were elevated with age (both P ≤ 0.001) and lower in runners than non-runners (P = 0.016 and P = 0.039, respectively). However, no age × training status interaction was observed for any of these parameters (Table 2).
| Characteristic                        | Young male non-runners | Young male runners | Middle-aged male non-runners | Middle-aged male runners | Age effect (P-value) | Training status effect (P-value) | Age × training status interaction (P-value) |
|--------------------------------------|------------------------|-------------------|-----------------------------|--------------------------|---------------------|-------------------------------|-----------------------------------------|
| Age (years)                          | 23 (21, 26)            | 24 (22, 26)       | 54 (52.56)                  | 56 (54, 58)              | ≤0.001              | 0.220                         | 0.577                                   |
| Resting heart rate (beats min⁻¹)     | 63 (58, 67)            | 45 (41, 49)       | 59 (54, 63)                 | 45 (41, 48)              | 0.259               | ≤0.001                        | 0.393                                   |
| Anthropometrics                      |                        |                   |                             |                          |                     |                               |                                         |
| Body mass (kg)                       | 82.0 (76.6, 87.5)      | 69.4 (64.9, 73.9) | 80.4 (74.9, 85.8)           | 67.7 (63.2, 72.2)        | 0.502               | ≤0.001                        | 0.999                                   |
| Height (cm)                          | 177.8 (174.4, 181.1)   | 180.6 (177.8, 183.3) | 175.3 (171.9, 178.6)       | 177.2 (174.4, 179.9)     | 0.058               | 0.127                         | 0.770                                   |
| BMI (kg m⁻²)                         | 25.9 (24.4, 27.4)      | 21.3 (20.0, 22.5) | 26.2 (24.7, 27.7)           | 21.5 (20.3, 22.8)        | 0.719               | ≤0.001                        | 0.992                                   |
| Training status                      |                        |                   |                             |                          |                     |                               |                                         |
| Training history (years)             | –                      | 7 (2.11)          | –                           | 27 (22, 31)              | ≤0.001              | –                             | –                                       |
| Weekly running (km)                  | –                      | 92 (82, 103)      | –                           | 53 (42, 64)              | ≤0.001              | –                             | –                                       |
| Recent 5 km PB (mins)                | –                      | 16:12 (15:33, 16:50) | –                           | 19:54 (19:11, 20:28)     | ≤0.001              | –                             | –                                       |
| $\dot{V}_{O_2,peak}$ (ml kg⁻¹ min⁻¹) | 37.7 (33.7, 41.7)      | 61.0 (57.7, 64.3) | 31.8 (27.8, 35.8)           | 51.3 (48.0, 54.6)        | ≤0.001              | ≤0.001                        | 0.294                                   |
| Brachial blood pressure              |                        |                   |                             |                          |                     |                               |                                         |
| SBP (mmHg)                           | 122 (117, 127)         | 113 (109, 117)    | 119 (114, 124)              | 118 (114, 122)           | 0.642               | 0.032                         | 0.101                                   |
| DBP (mmHg)                           | 72 (68, 75)            | 65 (62, 68)       | 77 (73.80)                  | 73 (70.76)               | ≤0.001              | 0.003                         | 0.458                                   |
| MAP (mmHg)                           | 86 (82, 89)            | 78 (75, 81)       | 91 (87.95)                  | 87 (84.94)               | ≤0.001              | ≤0.001                        | 0.217                                   |
| PP (mmHg)                            | 50 (46, 54)            | 48 (44, 51)       | 42 (38, 47)                 | 45 (41, 48)              | 0.110               | 0.955                         | 0.199                                   |

Data are reported as the group mean (95% confidence interval). Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; MAP, mean arterial pressure; PB, personal best; PP, pulse pressure; SBP, systolic blood pressure; and $\dot{V}_{O_2,peak}$, maximal aerobic capacity.
TABLE 2 Central haemodynamics, common carotid artery morphology and conventional indices of arterial stiffness for young male non-runners, young male runners, middle-aged male non-runners and middle-aged male runners

| Parameter                                      | Young male non-runners | Young male runners | Middle-aged male non-runners | Middle-aged male runners | Age effect (P-value) | Training status effect (P-value) | Age x training status interaction (P-value) |
|------------------------------------------------|------------------------|--------------------|------------------------------|--------------------------|----------------------|-------------------------------|------------------------------------------|
| Central blood pressure                         |                        |                    |                              |                          |                      |                               |                                          |
| cSBP (mmHg)                                    | 102 (97, 107)          | 95 (91, 99)        | 106 (101, 111)               | 106 (102, 110)           | ≤0.001               | 0.106                         | 0.126                                    |
| cDBP (mmHg)                                    | 74 (70, 77)            | 68 (65, 71)        | 75 (71, 79)                  | 71 (68, 75)              | 0.223                | 0.018                         | 0.535                                    |
| cMAP (mmHg)                                    | 86 (81, 90)            | 77 (73, 81)        | 87 (82, 92)                  | 84 (80, 88)              | 0.062                | 0.008                         | 0.192                                    |
| cPP (mmHg)                                     | 28 (26, 31)            | 27 (25, 30)        | 31 (28, 34)                  | 34 (32, 37)              | ≤0.001               | 0.451                         | 0.092                                    |
| CCA diameters and blood flow                   |                        |                    |                              |                          |                      |                               |                                          |
| Systolic diameter (mm)                         | 6.57 (6.26, 6.89)      | 6.45 (6.19, 6.71)  | 6.83 (6.52, 7.15)            | 6.90 (6.65, 7.16)        | 0.015                | 0.843                         | 0.500                                    |
| Diastolic diameter (mm)                        | 5.88 (5.57, 6.18)      | 5.66 (5.40, 5.91)  | 6.34 (6.03, 6.65)            | 6.26 (6.01, 6.52)        | ≤0.001               | 0.289                         | 0.605                                    |
| Mean diameter (mm)                             | 6.22 (5.94, 6.51)      | 6.12 (5.88, 6.36)  | 6.64 (6.36, 6.93)            | 6.47 (6.23, 6.70)        | 0.005                | 0.289                         | 0.763                                    |
| Distension (mm)                                | 0.49 (0.41, 0.58)      | 0.79 (0.72, 0.86)  | 0.49 (0.41, 0.58)            | 0.64 (0.57, 0.71)        | ≤0.001               | 0.004                         | 0.559                                    |
| Blood flow (ml min⁻¹)                          | 570 (500, 640)         | 602 (549, 655)     | 660 (586, 732)               | 615 (558, 673)           | 0.362                | 0.861                         | 0.238                                    |
| Conventional arterial stiffness indices         |                        |                    |                              |                          |                      |                               |                                          |
| aPWV (m s⁻¹)                                   | 5.8 (5.4, 6.3)         | 5.1 (4.7, 5.4)     | 7.4 (7.0, 7.9)               | 6.7 (6.3, 7.1)           | ≤0.001               | ≤0.001                         | 0.986                                    |
| E₀ (kPa)                                       | 33.1 (26.3, 39.9)      | 26.1 (20.4, 31.7)  | 57.5 (50.7, 64.3)            | 48.1 (42.5, 53.7)        | ≤0.001               | 0.016                         | 0.706                                    |
| β₂-Stiffness (cm² kPa)                         | 2.87 (2.3, 3.3)        | 2.43 (1.9, 2.9)    | 4.85 (4.3, 5.4)              | 4.16 (3.7, 4.6)          | ≤0.001               | 0.039                         | 0.634                                    |

Data are reported as the group mean (95% confidence interval). Abbreviations: aPWV, aortic pulse wave velocity; CCA, common carotid artery; cDBP, central diastolic blood pressure; cMAP, central mean arterial pressure; cPP, central pulse pressure; cSBP, central systolic blood pressure; and E₀, Peterson’s elastic modulus.
Common carotid artery two-dimensional strain parameters in the young male non-runners (YNR), young male runners (YR), middle-aged male non-runners (MNR) and middle-aged male runners (MR); (a) Peak circumferential strain (PCS; %), (b) systolic and (c) diastolic strain rate (S-SR and D-SR; 1/seconds). Data are reported as individual participant data points with corresponding group means (95% confidence interval). *Significant post hoc difference between groups ($P \leq 0.05$)

3.4 | Carotid artery 2D-Strain parameters

PCS, S-SR and D-SR were attenuated in middle-aged males when compared with young men (all $P \leq 0.001$). PCS and S-SR were elevated in runners when compared with non-runners ($P = 0.002$ and $P = 0.009$, respectively), but no age x training status interaction was observed for either parameter (Figure 1). In contrast, there was no main effect of training status on D-SR, but a significant age x training status interaction was observed ($P = 0.024$; Figure 1c). Subsequent pairwise analysis revealed that D-SR was significantly reduced in middle-aged runners compared with young runners (-0.26 [-0.37, -0.48] 1/s; $P \leq 0.001$), but no other differences were observed between the groups. All significant main effects of age and training status for PCS and S-SR remained after covariate adjustment for both CCA diastolic diameter and central mean arterial pressure, as did the main effect of age and age x training status interaction for D-SR.

3.5 | Relationship between CRF and carotid artery 2D-Strain parameters

Cardiorespiratory fitness was associated with PCS ($r^2 = 0.26$, $P \leq 0.001$) and S-SR ($r^2 = 0.25$, $P \leq 0.001$) when data from all groups were pooled, but there was no association between CRF and D-SR. When grouped by age (young versus middle-aged), the relationship between CRF and PCS remained in both groups (young, $r^2 = 0.18$; middle-aged, $r^2 = 0.18$; both $P = 0.015$; Figure 2a). Conversely, the relationship between CRF and S-SR remained in young males ($r^2 = 0.31$, $P \leq 0.001$) but was abolished in middle-aged males ($r^2 = 0.07$, $P = 0.133$; Figure 2b).

3.6 | Relationship between aPWV and carotid artery 2D-Strain parameters

The aPWV was associated with PCS ($r^2 = 0.32$, $P \leq 0.001$), S-SR ($r^2 = 0.32$, $P \leq 0.001$) and D-SR ($r^2 = 0.15$, $P = 0.002$) when data from all groups were pooled. When grouped by age (young versus middle-aged), the relationship between aPWV and PCS remained in the young and disappeared in the middle-aged group ($r^2 = 0.18$, $P = 0.016$ and $r^2 = 0.03$, $P = 0.381$, respectively; Figure 2c). Grouping by age had a similar effect on the relationship between aPWV and S-SR (young, $r^2 = 0.19$, $P = 0.013$; middle-aged, $r^2 = 0.000$, $P = 0.975$; Figure 2d). There was no relationship between aPWV and D-SR when grouped by age (young, $P = 0.389$; middle-aged, $P = 0.600$).

4 | DISCUSSION

The primary aim of this study was to examine the relationship between habitual endurance exercise and CCA 2D-Strain parameters in young and middle-aged men. Our main findings were as follows: (i) PCS, S-SR and D-SR were attenuated in middle-aged men compared with young men; and (ii) young and middle-aged runners exhibited elevated PCS and S-SR compared with non-runners. To our knowledge, this is the first study to demonstrate that habitual endurance exercise is associated with superior CCA 2D-Strain parameters in both young and middle-aged men, which provides new insight into the benefits of regular exercise on healthy arterial ageing.

In agreement with the literature, PCS, S-SR and D-SR were attenuated in healthy, middle-aged men compared with young counterparts (Bjällmark et al., 2010; Rosenberg et al., 2018), and this age-related decline occurred irrespective of training status. However, we also observed that PCS and S-SR were elevated in runners compared...
Figure 2: The relationship between common carotid artery (CCA) 2D-Strain parameters and peak oxygen uptake ($\dot{V}O_2^{\text{peak}}$) and aortic pulse wave velocity (aPWV). Panel A (peak circumferential strain [PCS; %]: Young: $r^2 = 0.18$. Middle-aged: $r^2 = 0.18$; both $P = 0.015$) and Panel B (systolic strain rate [S-SR; 1/seconds]: Young: $r^2 = 0.31$; $P \leq 0.001$. Middle-aged: $r^2 = 0.07$; $P = 0.133$) illustrate regression analyses examining the relationship between CCA 2D-Strain parameters and $\dot{V}O_2^{\text{peak}}$ in Young (○) and Middle-aged (▲) males. Panel C (PCS, Young: $r^2 = 0.18$; $P = 0.016$. Middle-aged: $r^2 = 0.30$; $P = 0.381$) and Panel D (S-SR, Young: $r^2 = 0.19$; $P = 0.013$. Middle-aged: $r^2 = 0.000$; $P = 0.975$) illustrate regression analyses examining the relationship between CCA 2D-Strain parameters and aPWV.

Healthy arterial ageing is characterized by alterations to the composition of the extracellular matrix within the arterial wall, including the degeneration of elastin fibres, as well as the accumulation of collagen, connective tissue and advanced glycation end-products, all of which promote arterial stiffening (Lakatta & Levy, 2003). In rat models, exercise training has been shown to improve the elastin-to-collagen ratio within the extracellular matrix of central arteries (Matsuda, Nosaka, Sato, & Ohshima, 1993), supporting the proposal that our observation of modulated 2D-Strain parameters in endurance-trained men might reflect favourable alterations to the elastic properties of the CCA. It should be noted that we did not observe an age × training status interaction for PCS or S-SR. However, our regression analysis revealed a similar linear relationship between CRF and PCS in both young and middle-aged men, whereas CRF was associated with S-SR only in young men and not in middle-aged men (Figure 2). Although more research across a wider age range is required, this distinction might indicate that the relative influence of habitual endurance training (high CRF levels) on PCS and S-SR differs with advancing age.

Indeed, it is plausible that the constraining effect of age-related accumulation of irreversible cross-linked collagen and advanced glycation-end products might limit the extent to which habitual endurance exercise can improve ‘global’ CCA elasticity in ageing men (Fujimoto et al., 2010; Lakatta & Levy, 2003). Exercise-mediated improvements in the relative contribution of elastin within the CCA extracellular matrix might be sufficient to increase the magnitude of circumferential deformation (PCS), but the accumulation of irreversible cross-linked collagen might hinder any concomitant improvement in the rate of deformation (S-SR). This supposition is...
supported by a recent animal study reporting that exercise training improved arterial elasticity solely by increasing elastin content despite negligible changes to collagen accumulation (Hanna et al., 2014). This constraining remodelling might also explain our surprising observation that the age-related decline in D-SR appears to be exacerbated in middle-aged male runners, in whom the inherent accumulation of cross-linked collagen coupled with a greater magnitude of deformation during systole gives rise to a blunted elastic transfer of potential energy and a slower rate of diastolic recoil. Clearly, without being able to obtain in vitro CCA samples in humans, attributing age- and training-induced changes in 2D-Strain parameters to alterations in the composition of the extracellular matrix is speculative. Nevertheless, our data demonstrate that 2D-Strain parameters provide new insight into the varied and intricate effects of habitual endurance exercise on CCA elasticity in young and middle-aged men.

Importantly, PCS and S-SR were elevated in young and middle-aged runners, despite displaying similar CCA diameter and blood flow to their untrained counterparts. Although not measured in the present study, it is well established that total blood volume and stroke volume increase with long-term endurance exercise training (Carrick-Ranson et al., 2014). However, it would seem that this increase in volume is not proportionately distributed to the carotid region at rest, presumably due to an unaltered demand for basal cerebral perfusion. Instead, we speculate that the increase in PCS represents a chronic training adaptation required to buffer repeated bouts of high CCA blood flow and normalize wall stress during intensive exercise. This proposition is consistent with the Law of Laplace and would explain the lack of association between PCS and CCA flow or diameter at rest. Furthermore, our ANCOVA confirmed that neither the age-related nor the habitual exercise-related differences in 2D-Strain parameters were influenced by CCA diastolic diameter. Likewise, all age-related differences in 2D-Strain parameters remained after covariate adjustment for central mean arterial pressure, as did all age-related differences in PWV.

4.1 Study limitations

Although this study benefited from a number of methodological strengths, including the comprehensive range of arterial stiffness measures and high training status of both the young and the middle-aged runners, there are some noteworthy limitations. First, our findings are restricted to the CCA and therefore cannot be applied systemically. Peripheral muscular arteries might be more susceptible to end-stage training than elastic central arteries (Dawson et al., 2008); therefore, 2D-Strain parameters should also be studied in peripheral vascular beds in the future. Second, the data reported are relevant only for healthy young and middle-aged men. Owing to recognized sex differences in haemodynamic regulation (Hart & Charkoudian, 2014) and vascular function (Green, Hopman, Padilla, Laughlin, & Thijssen, 2017), we acknowledge that women might display different age- and exercise-related changes in 2D-Strain parameters. Therefore, specific studies that are adequately powered to explore sex differences and examine whether sex hormones and/or the menopause influence the effect of habitual endurance exercise on healthy arterial ageing are warranted. Third, although the reported training volumes were sufficiently high and ecologically realistic for the respective age groups,
the middle-aged male runners demonstrated a lower training volume than the younger runners.

4.2 Conclusions

In conclusion, this is the first study to demonstrate that habitual endurance exercise is associated with enhanced PCS and S-SR in young and middle-aged men but does not influence D-SR in either age group. This new insight indicates that regular exercise is associated with comparable improvements in CCA 2D-Strain parameters in young and middle-aged men, but the age-related decline in PCS and S-SR might be more amenable to habitual endurance exercise than D-SR.

COMPETING INTERESTS

None declared.

AUTHOR CONTRIBUTIONS

The study was performed in the physiology laboratories in the Cardiff School of Sport and Health Sciences at Cardiff Metropolitan University. Conception of study design: J.S.T. and C.J.A.P. Data acquisition: J.S.T., R.N.L., D.J.W., T.G.D., B.A.C., M.B. and F.M.L. Data analysis: J.S.T. Data interpretation and drafting of final manuscript: J.S.T. and C.J.A.P. All authors critically revised the 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.

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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How to cite this article: Talbot JS, Lord RN, Wakeham DJ, et al. The influence of habitual endurance exercise on carotid artery strain and strain rate in young and middle-aged men. Experimental Physiology. 2020;105:1396–1407. https://doi.org/10.1113/EP088384