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Retrograde shift in carotid artery longitudinal wall motion after one-year follow-up in children

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HIGHLIGHTS

- Longitudinal arterial wall motion increases during a one-year follow-up in children.
- Longitudinal arterial wall motion tracks moderately well in children.
- Children exhibit sex-differences in vascular wall motion tracking over time.

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ABSTRACT

Background and aims: Cross-sectional studies suggest that arterial stiffness increases during childhood; however, this evidence stems from pressure-dependent arterial distension, while longitudinal movement of the arterial wall has not been explored. Carotid artery longitudinal wall motion (CALM) has been identified as a novel biomarker of vascular health in adults and may provide complementary biaxial wall information to vascular changes during childhood development. Accordingly, the purpose of this study was to assess how CALM changes and tracks over a one-year period in young children.

Methods: Children were recruited from the Health Outcomes and Physical activity in Preschoolers study (n = 114; 65 girls; age: 5.8 ± 0.9 years-old). CALM was measured at the left common carotid artery using ultrasound with speckle tracking.

Results: There were increases in CALM magnitudes over one-year follow-up, including systolic retrograde, diastolic, maximum, and total radial-axial displacement (all $p < 0.01$), with no differences between boys and girls. With the exception of systolic anterograde displacement, all CALM variables tracked better in girls than in boys, both individually (Spearman's ρ ranges: 0.49–0.61 *vs*. 0.25–0.47), as well as when split into tertile groups (Cohen's weighted κ ranges: 0.43–0.60 *vs*. 0.16–0.44), indicating overall moderate tracking ($\kappa > 0.40$) in the entire cohort.

Conclusions: CALM displacements change rapidly during childhood and track into pre-pubescence in a sex-specific manner. These findings suggest that CALM is influenced by individual factors that track consistently, and that similar to arterial stiffness, it may be valuable to examine the age-associated changes in CALM magnitudes to infer changes in child vascular health over time.

1. Introduction

Several high quality epidemiological studies have suggested that cardiovascular risk factors developed early in life may set a trajectory of health that persists into adulthood [1–3]. The utility of risk factor identification in childhood is highlighted by their propensity to track within children over time [4–6]. The existing evidence for risk factor tracking is primarily based on traditional risk factors such as blood lipids, blood pressure, and physical fitness, but has now also extended to emerging vascular risk factors such as intima-media thickness and arterial stiffness [7], which may mediate the link between traditional risk factors and the pathophysiology of atherosclerotic disease [8]. While traditional risk factors have been well studied, the stability of emerging risk factors in childhood, including vascular outcomes, is not well

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defined.

Pressure-dependent arterial distension has been widely used as an index of arterial stiffness [8], but there has been limited attention placed on the longitudinal (i.e., axial) displacement of the arterial wall. Carotid artery longitudinal wall motion (CALM) is described by bi-directional, tri-phasic wall displacements in the anterograde (i.e., in the direction of blood flow) and retrograde (i.e., opposite blood flow) directions, of which the maximal displacement is similar in magnitude to that of radial-plane distension [9,10]. Recent evidence suggests that the magnitude of CALM is related to cardiovascular risk markers independent of vascular stiffness or wall thickness in older healthy and older clinical populations [11–13]. However, there have been few longitudinal investigations that detail either the stability of wall motion or the propensity for change over time [14], and none in children – a population for which identification of early changes in vascular health may have important consequences on cardiovascular risk in adulthood [15].

Given the rapid age-related changes in anthropometrics and cardiovascular outcomes in young children [16–18], changes in CALM pattern and magnitude may occur over an accelerated timeline, potentially indicating dysfunction by deviations from natural aging trajectories; although indications of stability have not been previously established for CALM outcomes. Therefore, the purpose of this study is to determine how CALM variables track over a one-year period in young children and whether CALM magnitude changes over this short timeframe. We hypothesized that individual patterns will track well over time, though the systolic and diastolic phases of CALM will diminish in magnitude, extending our previous observations in older adults [19] to reveal a steady decline in CALM displacement magnitudes over the lifespan.

2. Materials and methods

2.1. Participants and ethical approval

Participants were recruited from the Health Outcomes and Physical activity in Preschoolers (HOPP) study (n = 418), for which the general rationale and methodology have been previously described [20]. In brief, 3-, 4-, and 5-year old children were observed once a year, for three consecutive years, for measurement of physical activity habits and cardiovascular health. In a subset of participants (n = 154), higher frame rate vascular ultrasound imaging was performed for acquisition of CALM images in year two and three of the longitudinal study. Forty participants were excluded due to poor data quality (primarily due to poor echogenicity of the far common carotid artery wall, high echo backscatter, out of plane motion, or angled segments of the arterial wall), resulting in a final sample of 114 participants. All methods and procedures conform to the ethical guidelines of the 1975 Declaration of Helsinki, and were approved by the Hamilton Integrated Research Ethics Board. All testing was conducted in the Vascular Dynamics Lab at McMaster University. The parents and/or guardians of all participants gave verbal and written consent prior to participation in this study.

2.2. Experimental design

Participants were assessed at two time points, separated by 12 ± 1 months. Height was measured without shoes to the nearest 0.1 cm using a calibrated stadiometer and body mass was measured without shoes and in light clothing to the nearest 0.1 kg with a digital scale [20]. BMI z-scores and weight classification were determined from U.S. Centre for Disease Control and Prevention Data [16]. At each visit, participants were instructed to rest supine for 10 min prior to vascular data collection. Through the entirety of the session, a movie was projected onto the ceiling to ensure participants remained supine throughout the protocol. Participants were continually monitored with single-lead ECG using a commercially-available data acquisition system (PowerLab Model ML 132, AD Instruments, Colorado Springs, CO, USA) and analysis software (LabChart, AD Instruments, Colorado Springs, CO, USA). Brachial blood pressure was assessed in triplicate at the right arm immediately after vascular measurements with an automated oscillometric device in the supine position (Dinamap Pro 100; Critikon LCC, Tampa, USA).

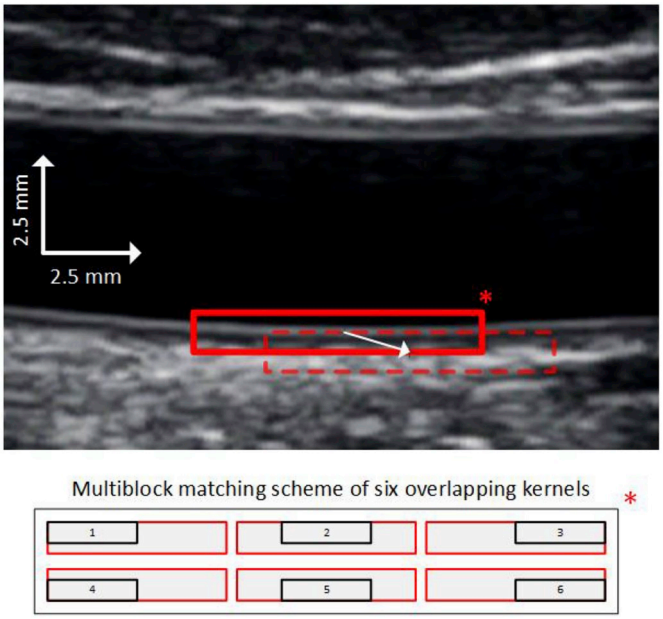

Fig. 1. Schematic of image processing using a custom vascular speckle-tracking algorithm in a representative pediatric common carotid artery image.
The solid red box represents the entire multiblock matching scheme, which contains six overlapping kernels for robust 2D motion tracking. The arrow simulates the tracking window shifting over consecutive frames to after finding the highest tracking coefficient of black and white pixels. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.3. Carotid artery longitudinal wall motion

CALM was assessed at the left common carotid artery, 2–5 cm proximal to the carotid bifurcation using a 12 MHz linear array probe attached to a high-resolution ultrasound (Vivid q; GE Medical Systems, Horten, Norway). At least two cardiac cycles were acquired at > 90 fps at each session [21]. Imaging location was standardized by landmarking the carotid bifurcation to the left of the image in all scans. Images were analyzed using a custom speckle-tracking program (MATLAB, The MathWorks, Natick, MA, USA) (Fig. 1) [10]. Cardiac cycles were identified by the QRS complex from the single-lead ECG trace on the ultrasound images, and analysis was performed on a beat-by-beat basis to minimize the impact of cumulative drift on CALM outcomes. As children were freely breathing during acquisition, cumulative 'drift' was observed with the artery wall not returning to the reference point at the end of the cardiac cycle. To address this drift, a regression line was fit from the reference position to the final point in the cardiac cycle, which was subtracted from the raw radial and longitudinal motion data to remove cumulative bias, similar to methods recommended for 2D speckle tracking echocardiography [22].

CALM traces were plotted for manual segmentation of motion phases of the intima-media complex (Fig. 3B), as previously described [19,23]. In brief, systolic anterograde CALM was defined as the phase between the first systolic anterograde movement to the peak systolic anterograde displacement, systolic retrograde CALM was defined as the phase between the peak systolic anterograde displacement to the peak retrograde displacement, and diastolic CALM was defined as the phase between the peak retrograde displacement and the early diastolic

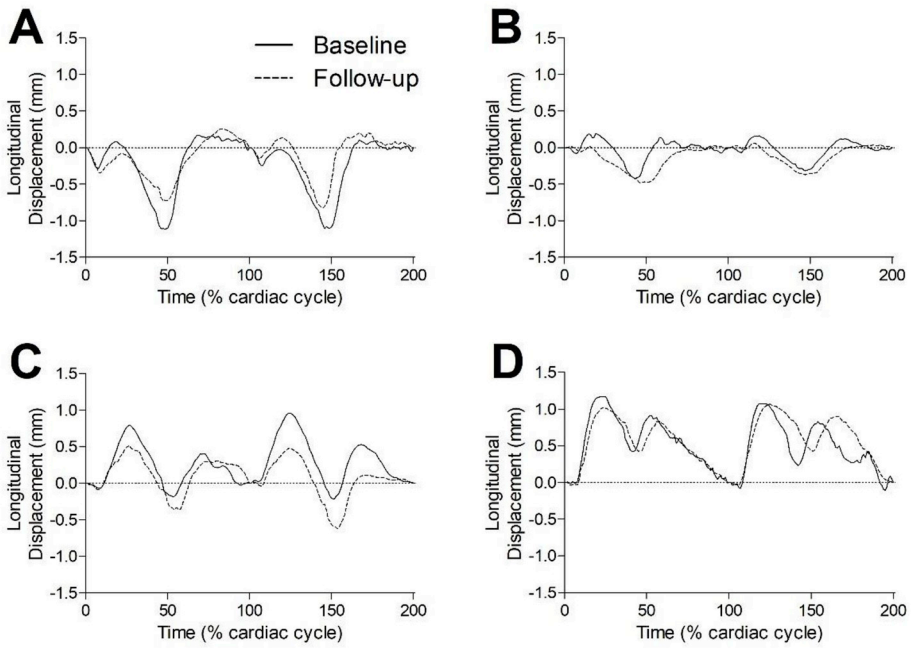

Fig. 2. Representative individual longitudinal displacement traces demonstrating between-subject variability, but highly reproducible data from baseline (solid) to one-year follow-up (dashed).
Motion corrected data from two cardiac cycles is presented, with linear bias removed from each individual cardiac cycle at the QRS complex. (A) Boy at ages 5 and 6; (B) boy at ages 6 and 7; (C) girl at ages 6 and 7; and (D) girl at ages 6 and 7.

anterograde plateau. Axial length, radial length, and radial-axial length were calculated as the total distance (axial, radial, and combined directions) that the arterial wall travels over a cardiac cycle [24]. To calculate peak instantaneous diastolic velocity and acceleration, motion traces were digitally filtered with a 2nd order, dual pass Butterworth filter with a conservative cut-off frequency of 10 Hz to account for degradation in the speckle-tracking normalized cross-correlation coefficient later in the cardiac cycle [25]. To facilitate group-averaging for figures, CALM displacements were linearly interpolated to 100 discrete points to account for variable cycle lengths.

2.4. Statistics

Statistical analyses were performed using IBM SPSS Statistics for Macintosh Version 20.0.0 (IBM, Armonk, NY, USA). Data were assessed for normality using the Shapiro-Wilk test. Two methods were used to assess tracking of CALM outcomes to account for measurement error [26,27]: individual tracking using Spearman's rank correlation and tertile tracking using Cohen's weighted kappa (κ) with squared differences [28]. Multiple methods were used to account for biological variability, which may have affected the unweighted Spearman's rank order correlation. The strength of tracking using Cohen's κ was assessed as per Twisk et al. (1994): > 0.75 good tracking, > 0.4 moderate tracking, < 0.4 poor tracking. The relationship between changes in CALM and changes in anthropometrics from baseline to follow-up were assessed with Pearson's correlation. We also examined the differences between sexes over time using a 2 × 2 (sex x time) mixed factors ANCOVA (covariates: change in BMI, change in mean arterial pressure, and change in heart rate) with Tukey's HSD *post hoc* tests to evaluate significant effects. For all analyses, the acceptable level of error was set at $\alpha = 0.05$.

3. Results

The participant characteristics are presented in Table 1. Representative examples of longitudinal wall motion are displayed in Fig. 2. While there exists large inter-subject variability in trace shape and segmented displacement magnitudes, intra-subject variability over time is small and the general shape of the longitudinal trace is preserved. The group-averaged radial displacement pattern (Fig. 3A) exhibited the expected expansion and recoil associated with single-wall arterial wall motion. The group-averaged longitudinal displacement pattern (Fig. 3B) exhibited the expected bi-directional, tri-phasic motion pattern, although all traces were noticeably shorter in duration compared to adult examples, due to the higher resting heart rate (~80 bpm *vs.* 60–70 bpm as reported in adult studies [19]). Two-dimensional motion loops were generated to represent both the radial and axial wall displacement (Fig. 3C), demonstrating a 'figure-eight' pattern as the arterial wall extends, and simultaneously oscillates longitudinally around the central reference position.

After one-year follow-up, radial-axial motion loops exhibited a downward-left shift with the majority of motion differences occurring after the initial anterograde systolic motion. Single-wall radial-plane motion decreased in follow-up in girls only, indicative of less arterial wall distension during systole (0.57 ± 0.15 to 0.51 ± 12 mm; $p < 0.05$). Specific to the longitudinal plane, the CALM pattern retained its general shape, with no change in the magnitude of the initial systolic anterograde displacement ($p = 0.21$). There were no effects of sex for any changes in CALM magnitude observed over time, so we report the following main effects for time. There were increases in the magnitude of systolic retrograde CALM displacement, diastolic CALM displacement, maximum CALM displacement, radial-length, axial-length, and radial-axial length (all $p < 0.01$), which were accompanied by increased maximal instantaneous velocity ($p < 0.01$) and acceleration ($p = 0.01$) of the diastolic return to the reference position (Table 1). Radial-axial length, and axial length increased at follow-up ($p < 0.01$), with no change in radial length ($p = 0.11$). Speckle tracking success, as indicated by the average normalized cross-correlation coefficient, was improved in the second year of the study ($p = 0.05$).

Tracking was assessed at the individual level using Spearman's ρ correlation, and at the group level by determining the degree of movement between tertiles using Cohen's weighted κ statistic (Table 2). Overall, Spearman's ρ ranged from 0.44 to 0.52 (all $p < 0.01$) among variables, indicating moderate individual tracking. When split by sex, tracking of systolic anterograde CALM displacement was stronger in boys (ρ = 0.61) than in girls (ρ = 0.39), but tracking of the remainder of CALM variables was stronger in girls (ρ: 0.49 to 0.61) than in boys (ρ: 0.25 to 0.47). Tertile movement describes whether individuals remain in the same tertile or move within the group distribution at follow-up

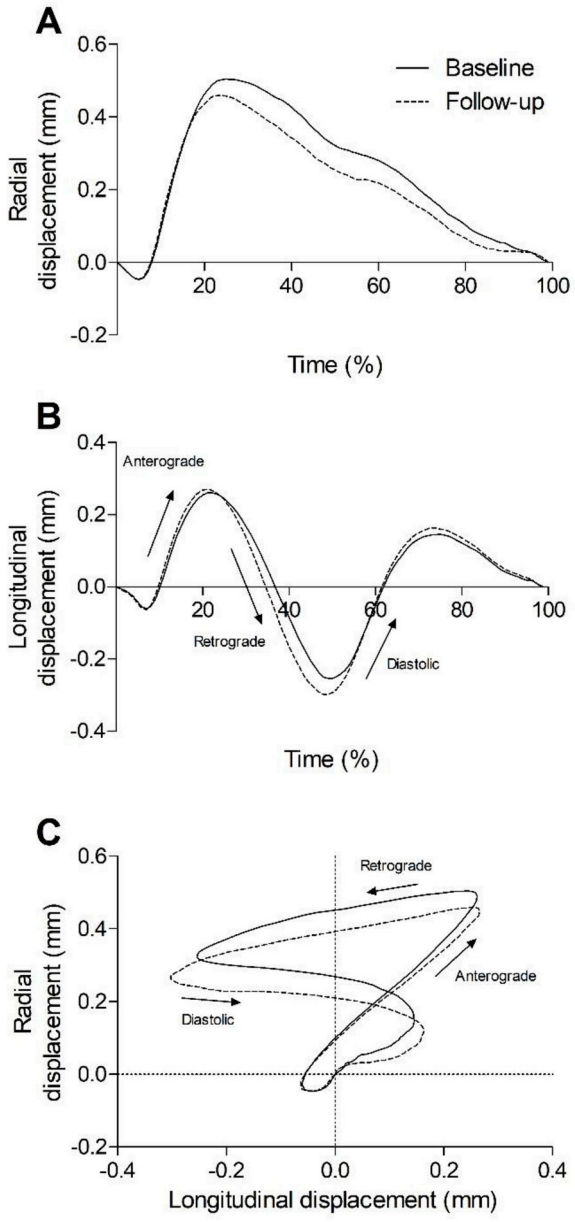

Fig. 3. (A) Carotid artery wall radial, (B) longitudinal, and (C) biaxial wall displacement, at baseline (solid) and follow-up (dashed).
Biaxial wall displacement starts at the reference position [0,0], with arrows indicating the direction of motion over time and the relative phase of the CALM trace. Motion traces were interpolated to a single cardiac cycle to present data as a group average for the entire sample.

assessment compared to baseline. Among all CALM variables, 40–55% of individuals stayed within the same tertile; in comparison, it would be expected that 33% would stay in their tertile due to random chance alone. Cohen's weighted κ evaluates percentile movement with a coefficient value by considering how many tertiles individuals changed upon follow-up (e.g., moving from the 1st to the 3rd tertile is weighted more than moving from the 1st to the 2nd tertile). Similar to Spearman's ρ, systolic anterograde CALM displacement tracked better in boys (κ = 0.63) than in girls (κ = 0.26), while the remainder of CALM variables tracked better in girls (κ: 0.43 to 0.60, moderate tracking) than in boys (κ: 0.16 to 0.44, poor-to-moderate tracking). Overall, moderate tracking was predominantly observed for the entire cohort.

Neither the change in CALM outcomes nor radial wall displacement was related to changes in height, body mass, BMI z-scores, blood pressures, heart rate, or with each other (all $p > 0.05$). There were also no correlations at baseline or follow-up, other than that baseline radial wall displacement was correlated with baseline mean arterial blood pressure ($r = 0.21$, $p = 0.03$).

4. Discussion

After a one-year follow-up period in young children (4–7 years of age), we observed changes in motion of both the longitudinal and radial planes of the CCA wall, highlighted by greater longitudinal displacements over time. Despite changes in longitudinal displacement magnitude, CALM tracked well within the entire cohort, though most CALM outcomes tracked better in girls than boys. These results suggest that CALM is not merely a product of random vascular variability, but is likely influenced by factors unique to each individual. These findings fit well with previous CALM literature, indicating longitudinal motion is a stable index of arterial structure that may provide valuable indications of vascular health over longer term monitoring periods such as the one-year time period included in this study.

Tracking analyses are valuable to determine the stability of an outcome over time [26]. Tracking in childhood is of particular importance, as longitudinal studies suggest that risk factors acquired early in life track well into adulthood to contribute to cardiovascular disease burden later in life [6]. Previous cardiovascular tracking studies within the childhood period have identified moderate tracking (κ > 0.40) of blood pressure [5], markers of metabolic syndrome [29] and fitness [27], although no studies to our knowledge have investigated tracking of vascular health indicators. We observed moderate tracking in CALM for maximal wall displacement and diastolic outcomes. A possible sex-difference in tracking may reflect differences in vascular health during childhood between boys and girls, where boys present with thicker arterial walls [30] and increased brachial-ankle pulse wave velocity [31] for the same age. While it is difficult to interpret these findings in the context of a 1-year follow-up, it is reasonable to expect consistent trends during a period of linear growth up to puberty. Given that CALM may represent vascular health information independent of traditional arterial distension [11,12,19], its measurement may be a valuable tool to complement the assessment of vascular health and traditional cardiovascular risk factors.

It is now apparent that radial (expansion) and axial (longitudinal) wall motion may represent unique, independent aspects of vascular structure. Whereas arterial expansion is tightly coupled to both blood pressure [32] and intrinsic arterial wall properties, CALM exhibits a bi-directional, tri-phasic pattern, for which its regulation remains undetermined [33–35]. The pressure-dependence of CALM is unclear, as we have previously demonstrated an absence of longitudinal motion changes in response to cold pressor test increases in blood pressure in humans [33], although Ahlgren et al. (2012) have shown large changes in response to catecholamine infusion in a porcine model [36]. In the present study, we did not observe any correlation between changes in CALM outcomes and changes in either blood pressure or single-wall radial displacement, which may indicate a degree of independence between the two motion parameters. Cross-sectional studies have suggested that CALM is a novel biomarker of vascular health that changes with age and disease, similar to traditional markers of vascular stiffness and wall thickness [11–13]; and more recently, we have shown that systolic retrograde and maximum CALM displacement are weakly related to whole-body pulse wave velocity [37]. In comparison to previous cross-sectional reports of CALM in younger and older adults [11,19,24,38], children exhibit the same general pattern with greater magnitude of individual motion segments (anterograde: 0.41 mm; retrograde: 0.66 mm) as well as maximal displacement (0.74 mm). Notably, the vascular wall in children travels a much greater axial-radial distance than middle-aged adults (radial-axial length 2.6 mm *vs.* 1.5 mm, as reported in Taivainen et al., 2017), which appears to be dominated by changes in the axial direction. Previous cross-sectional

Table 1
Participant characteristics at baseline and follow-up (N = 114).

Outcome	Baseline		Follow-up	
	Boys	Girls	Boys	Girls
n	49	65	49	65
Age (yr)*	5.8 ± 0.8	5.8 ± 0.9	6.8 ± 0.8	6.8 ± 0.9
Height (cm)*	115.3 ± 7.0	115.3 ± 7.9	121.8 ± 7.2	121.7 ± 8.1
Body mass (kg)*	20.6 ± 3.2	20.6 ± 3.7	23.0 ± 3.7	23.3 ± 4.5
Body mass index (kg/m^2)	15.4 ± 1.2	15.4 ± 1.4	15.4 ± 1.2	15.6 ± 1.6
Body mass index z-score	−0.15 ± 0.90	−0.08 ± 0.96	−0.25 ± 0.92	−0.07 ± 0.92
Overweight/obesity (%)	5 (10)	9 (14)	4 (8)	7 (11)
Resting heart rate (bpm)*	82 ± 8	82 ± 10	79 ± 10	79 ± 10
Systolic blood pressure (mmHg)*	97 ± 8	95 ± 7	99 ± 7	97 ± 7
Diastolic blood pressure (mmHg)	55 ± 5	56 ± 5	55 ± 5	57 ± 5
Mean arterial pressure (mmHg)*	71 ± 5	72 ± 5	73 ± 6	74 ± 6
CALM outcomes				
Ant. CALM (mm)	0.43 ± 0.27	0.40 ± 0.21	0.47 ± 0.27	0.40 ± 0.19
Ret. CALM (mm)*	0.66 ± 0.27	0.66 ± 0.25	0.76 ± 0.29	0.70 ± 0.29
Dias. CALM (mm)*	0.54 ± 0.28	0.58 ± 0.27	0.63 ± 0.28	0.63 ± 0.28
Max. CALM (mm)*	0.74 ± 0.29	0.74 ± 0.26	0.85 ± 0.29	0.79 ± 0.29
MIDV (mm/s)*	6.17 ± 3.28	6.94 ± 3.01	7.02 ± 2.94	7.14 ± 4.48
MIDA (mm/s^2)*	183 ± 84	188 ± 66	201 ± 80	178 ± 157
Axial length (mm)*	2.28 ± 0.73	2.18 ± 0.70	2.68 ± 0.69	2.42 ± 0.61
Radial length (mm)	1.38 ± 0.33	1.39 ± 0.42	1.59 ± 0.53	1.41 ± 0.52
Radial-axial length (mm)*	2.95 ± 0.75	2.89 ± 0.77	3.47 ± 0.86	3.12 ± 0.70
Radial displacement (mm)	0.58 ± 0.15	0.57 ± 0.15	0.59 ± 0.12	0.51 ± 0.12†
NCC*	0.88 ± 0.04	0.89 ± 0.04	0.89 ± 0.04	0.90 ± 0.04

Ant. CALM, systolic anterograde CALM displacement; CALM, carotid artery longitudinal wall motion; Dias. CALM, diastolic CALM displacement; Max. CALM, maximal CALM displacement; MIDA, maximal instantaneous diastolic acceleration; MIDV, maximal instantaneous diastolic velocity; NCC, normalized cross-correlation coefficient; Ret. CALM, retrograde CALM displacement.
*$p < 0.05$ baseline different from follow-up. †$p < 0.05$ different from girls' baseline.

Table 2
Tracking statistics for CALM outcomes.

Outcome	Spearman ρ			Cohen's weighted κ		
	Overall	Boys	Girls	Overall	Boys	Girls
Ant. CALM	0.51*	0.61*	0.39*	0.41*	0.63*	0.26*
Ret. CALM	0.44*	0.25	0.56*	0.36	0.16	0.48*
Dias. CALM	0.48*	0.47*	0.54*	0.55*	0.44*	0.43*
Max. CALM	0.50*	0.35*	0.61*	0.49*	0.34	0.60*
MIDV	0.52*	0.46*	0.54*	0.45*	0.34*	0.50*
MIDA	0.44*	0.40*	0.49*	0.37*	0.28	0.43*
Radial-axial length	0.53*	0.51*	0.57*	0.48*	0.44*	0.58*

Ant. CALM, systolic anterograde CALM displacement; CALM, carotid artery longitudinal wall motion; Dias. CALM, diastolic CALM displacement; Max. CALM, maximal CALM displacement; MIDA, maximal instantaneous diastolic acceleration; MIDV, maximal instantaneous diastolic velocity; Ret. CALM, retrograde CALM displacement.
*$p < 0.05$.

studies have indicated that maximum CALM displacement decreases with age [11,19], and that there may be a shift towards an anterograde dominant pattern with older age and atherosclerotic burden [39,40]. However, contrary to our initial hypothesis, our findings in children suggest an inverted-U model for changes in displacement magnitude with age, as we observed an increase in CALM displacement magnitudes over a one-year time period in childhood. This pattern has also been observed in healthy adult populations, with a nadir observed between 25 and 34 years of age [40]. An important point of note is that central hemodynamics remain in flux during childhood, which might impact the increase in displacement magnitude over time. Children had decreased heart rate, and increased blood pressure during the follow-up visit, consistent with the normal trajectory of cardiovascular aging [41,42]. While previous experimental studies have not demonstrated the impact of small (i.e., heart rate: -3 bpm, blood pressure: +2 mmHg) changes in hemodynamics [33,35], we can cannot exclude this modifying factor in our interpretation of the data, although we attempted to correct for these influences as covariates in our model. We have recently demonstrated weak correlations between CALM and arterial stiffness measured by whole-body pulse wave velocity in a larger cross-sectional cohort from the HOPP study [37]. This finding suggests that factors other than conventional arterial stiffness might be associated with CALM in children; additional biological and non-biological determinants of changes in the CALM pattern remain to be investigated in children and may serve as important future steps to this report.

In the current study, changes in CALM magnitude were detected after one year of observation. Previous reports indicate that arterial stiffness also increases across childhood and adolescence [43,44], however, there is evidence that pulse wave velocity remains relatively consistent in children between the ages of 3 and 10 years, suggesting that changes in CALM do not follow similar changes in arterial stiffness [45]. It is possible that the observed changes in CALM may be attributed to the rapidly shifting composition of the arterial wall in childhood, thereby impacting intrinsic longitudinal tension of the intima-media complex. Forensic studies in longitudinal pre-strain (i.e., the stretch, or longitudinal tension, in the arterial wall) indicate an exponential decrease with age from young adulthood [46], but it is unknown how pre-strain develops during childhood. As an ancillary finding, we observed that vascular speckle-tracking success improved in the second year of assessment, potentially indicating ultrasound texture-based changes in arterial wall composition [47]. A retrograde shift in the CALM pattern in children may be related to changes in wall composition and longitudinal pre-strain with aging, although pre-clinical models are needed to fully elucidate the impact of extracellular remodelling on longitudinal strain.

4.1. Limitations

Children were not asked to hold their breath during data acquisition due to compliance concerns. As breathing has been previously shown to affect CALM measures [9], we corrected for speckle drift attributed to both breathing artifact and speckle decorrelation by regressing the bias back to the reference point, assuming linear cumulative drift over a

single cardiac cycle. While we are unable to confirm constant velocity and direction of breathing influence, the effect of drift was also minimized by analyzing single cardiac cycles, rather than multiple cycles with the same reference kernel position. These correction techniques have previously been employed in commercial speckle tracking applications [22]. Respiratory artifact is known to cyclically affect the magnitude of arterial distension and pulse pressure beyond measurement drift, and while inspiratory *vs.* expiratory influence has not been examined with CALM, we cannot exclude the possibility that breathing impacted the measurement sensitivity in this study. Finally, while the radial-axial length outcome has shown utility in previous cross-sectional investigations [38], it should be noted that single-wall distension may not be a valid surrogate for distension measured between two walls, precluding the calculation of traditional estimates of arterial stiffness using this method.

The study of CALM is steadily growing, with open source software now available for speckle-tracking analysis [48], leading to new investigations examining how longitudinal arterial wall motion may relate to vascular health and aging. This is the first longitudinal study to report changes in CALM magnitude over time in children, suggesting an increase in CALM displacement magnitudes over a 1-year period in children. These novel findings refute the notion that CALM occurs by a set of randomly varying cardiovascular interactions, and instead suggest that CALM is influenced by individual factors that track consistently over time, such as arterial stiffness or wall thickness. Accordingly, it may be valuable in future studies to examine whether chronic changes in CALM represent a novel vascular biomarker to infer cardiovascular disease risk across the lifespan.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Author contributions

J.A. and N.P. contributed to the acquisition and analysis of the data. J.A., N.P., B.T., and M.M. contributed to the conception of the study design, interpretation and critical review of the data, as well as the drafting of the final manuscript. B.T. and M.M. acquired the funding for the study. All authors approved the final version of the manuscript.

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