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REVIEW

Integrative Cardiovascular Physiology and Pathophysiology

Physiological basis for longitudinal motion of the arterial wall

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Abstract

As opposed to arterial distension in the radial plane, longitudinal wall motion (LWM) is a multiphasic and bidirectional displacement of the arterial wall in the anterograde (i.e., in the direction of blood flow) and retrograde (i.e., opposing direction of blood flow) directions. Although initially disregarded as imaging artifact, LWM has been consistently reported in ultrasound investigations in the past decade and is reproducible beat-to-beat, albeit with large interindividual variability across healthy and diseased populations. Emerging literature has sought to examine the mechanistic control of LWM to explain the shape and variability of the motion pattern but lacks considerations for key foundational vascular principles at the level of the arterial wall ultrastructure. The purpose of this review is to summarize the potential factors that underpin the causes and control of arterial LWM, spanning considerations from the arterial extracellular matrix to systems-level integrative theories. First, an overview of LWM and relevant aspects wall composition will be discussed, including major features of the multiphasic pattern, arterial wall extracellular components, tunica fiber orientations, and arterial longitudinal prestretch. Second, current theories on the systems-level physiological mechanisms driving LWM will be discussed in the context of available evidence including experimental human research, porcine studies, and mathematical models. Throughout, we discuss implications of these observations with suggestions for future priority research areas.

arterial stiffness; blood pressure; longitudinal prestretch; tunica media; ventricular vascular coupling

INTRODUCTION

Pressure-based radial distension of arterial walls has been widely studied in cardiovascular research, yielding a deep understanding of the regulatory mechanisms that control both chronic and dynamic changes in arterial diameter (i.e., blood pressure, heart rate, vascular tone, wall thickness, arterial stiffness, etc.) (1–6). Distension is often studied in the context of circumferential stress and strain. However, arteries are three-dimensional structures that exhibit unique static and dynamic tissue properties in not only the circumferential but also longitudinal and radial directions.

Longitudinal wall motion (LWM) is a multiphasic and bidirectional displacement of the arterial wall with both anterograde (i.e., in the direction of blood flow) and retrograde (i.e., opposing the direction of blood flow) displacements in the longitudinal plane. LWM has traditionally been considered insignificant compared with the radial distension and was previously disregarded as a motion artifact due to breathing (7). This notion of negligible LWM has remained for decades; for example, McDonald's Blood Flow in Arteries noted there to be "very little, if any, longitudinal movement of the artery during passage of the pulse wave," which was indicated as the basis for investigations into arterial tethering (3). Experimental acknowledgment of LWM first appeared in 2001 when Tozzi et al. (8) made the first detailed observations on LWM by suturing reflective beads to canine aortas. Hereafter, an increasing interest in LWM has led to technical advancements in imaging techniques for noninvasive measurement and analysis, and more detailed observations on displacement phases in healthy and clinical human populations. Recent research has shown that LWM is reproducible beat-to-beat and retains unique individual patterns during up to a year of repeat observations (9, 10). In addition, LWM magnitude diminishes from the central to the peripheral arteries (11), as well as along the length of a single vessel (12), suggesting influence of the material composition of vessel walls, of perivascular tethering, as well as confounding radial-axial strain coupling due to changing vessel diameters. Consistent with this view, central arterial LWM (i.e., at the common carotid artery) varies with age and health status (13), showing similar trends as seen in conventional measures of central arterial stiffness and function (e.g., patients with increased arterial stiffness show reduced LWM) (14). The current clinical findings and inference from observational studies have been reviewed elsewhere (15).

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From a physiological perspective, there is little available literature to explain the biological etiology and regulatory physiological mechanisms behind LWM. Fundamental ex vivo and in situ studies have examined the anisotropic behavior of the arterial wall in isolation [i.e., how the properties of the material and their distensibility depends on the direction of the force (16)]. However, these key principles (e.g., longitudinal prestretch, extracellular matrix, fiber orientations, etc.) have not yet been linked to our current understanding of LWM (17–19).

The purpose of this review is to summarize the potential factors that underpin the causes of arterial LWM, spanning considerations from the arterial extracellular matrix to systems-level integrative theories. First, an overview of LWM and relevant aspects of wall composition will be discussed, including major features of the multiphasic LWM pattern, arterial wall extracellular components, fiber orientations, and longitudinal prestretch. Second, current theories on the systems-level physiological mechanisms driving LWM will be discussed in the context of available evidence. Throughout, we discuss implications of these observations with suggestions for future priority research areas that will contribute to our understanding of the vascular physiology behind LWM. Most, if not all human data regarding LWM are acquired from the intima-media complex in the common carotid artery (CCA); therefore, this review will discuss longitudinal motion in reference to the CCA unless otherwise specified.

GENERAL PHASES OF LONGITUDINAL WALL MOTION

Longitudinal wall motion is bidirectional (e.g., anterograde and retrograde) and multiphasic in nature (11) (Fig. 1). Three distinct phases have been consistently identified: systolic anterograde LWM, systolic retrograde LWM, and diastolic LWM (9, 11, 20–24). Systolic anterograde LWM refers to the initial displacement occurring in the same direction as blood flow. As the forward blood velocity wave reaches its peak, a systolic retrograde LWM phase begins in the direction opposing blood flow. During diastole, the final anterograde LWM phase occurs, resulting in a gradual return to the reference position, often oscillating around a set point. Some argue that the diastolic LWM phase can be subdivided into a secondary anterograde LWM and a return to equilibrium phase (25) but up to now, this segmentation has not been standardized. Recent analyses have also suggested more subtle phases of motion throughout the cardiac cycle, including a brief anterograde displacement or shoulder during the retrograde displacement (i.e., *phase X*), as well as a brief end-diastolic retrograde movement immediately before the first systolic displacement (i.e., *phase W*) (25, 26). *Phases X* and *W* are more prominent in older adults and are detected to a lesser extent in younger adults. Given that these additional phases are not universally observed, further research is necessary to determine their significance in generalized wall motion patterns.

Significant variation in LWM exists between individuals (9, 11, 22), most notably across different age groups (13, 25) and health status (27). Despite the noted group differences, in most individuals, LWM phases follow a similar multiphasic pattern with most of the variability occurring in phase amplitude. Our research group has accumulated a collection of LWM traces from a range of healthy adults using similar methodology; Fig. 2 combines cycle-averaged ECG-gated motion traces from healthy younger and older adults to demonstrate the above noted key patterns. Although there is clear variability between waveform amplitudes, the general retrograde deflection is conserved. These observations support the notion that LWM is not random motion variability, and that central governing factors control longitudinal wall behavior in humans. The remainder of this review investigates key observations in LWM that point toward control factors and the impact of vascular structure and function on motion patterns.

SPECIFIC OBSERVATIONS FROM LONGITUDINAL WALL MOTION STUDIES

Beyond the general LWM pattern, previous studies have made a number of important observations that aid our understanding of the physiological regulation of the LWM pattern. The following sections provide brief overviews of these key findings to contextualize the role and impact of the arterial extracellular matrix.

Motion Synchronous with Radial Displacement

In addition to LWM being of similar magnitude as radial distension (21), systolic anterograde LWM occurs simultaneously with radial distension, whereas systolic retrograde LWM is synchronous with decreases in arterial diameter (11) (also cf. Fig. 1). Furthermore, there is a temporal association between *phase X* which occurs during systolic retrograde LWM, and the dicrotic notch of the distension wave (25), suggesting coupling between longitudinal and radial displacements, possibly mediated by the distending pressure waveform. Indeed, initial experiments in porcine models suggest a strong dependence of LWM on pressure, as assessed using pressor interventions (9, 28, 29). Visual representations of the radial-longitudinal relationship can be observed in 2-D motion loops, creating a "figure 8" shape (Fig. 3) that combines both longitudinal and radial displacements occurring over the cardiac cycle (21, 24, 29–31). Based on this suggested 2-D coupling, it is likely that two-dimensional motion with both longitudinal and radial wall motion is a more appropriate way of examining the arterial wall, as, e.g., the total wall motion path length can be calculated in 2-D space (24).

Intramural Shear Strain

LWM is not uniform throughout the arterial wall layers. The intima-media complex displaces more than the adventitial layer or surrounding tissue, creating a shear strain between wall layers (11). With the advent of higher resolution speckle-tracking algorithms (32), the intima-media complex, adventitia, and surrounding tissue can be individually tracked to produce relative motion comparisons and report a strain angle between layers. Strain angles ranging from 0.36 ± 0.26 radians ($\sim 20^\circ$) (11) to 0.82 ± 0.17 radians ($\sim 46^\circ$) (32) have been reported, with the largest amount of shear strain occurring in a small section around the transition between the media and adventitia, although large variation

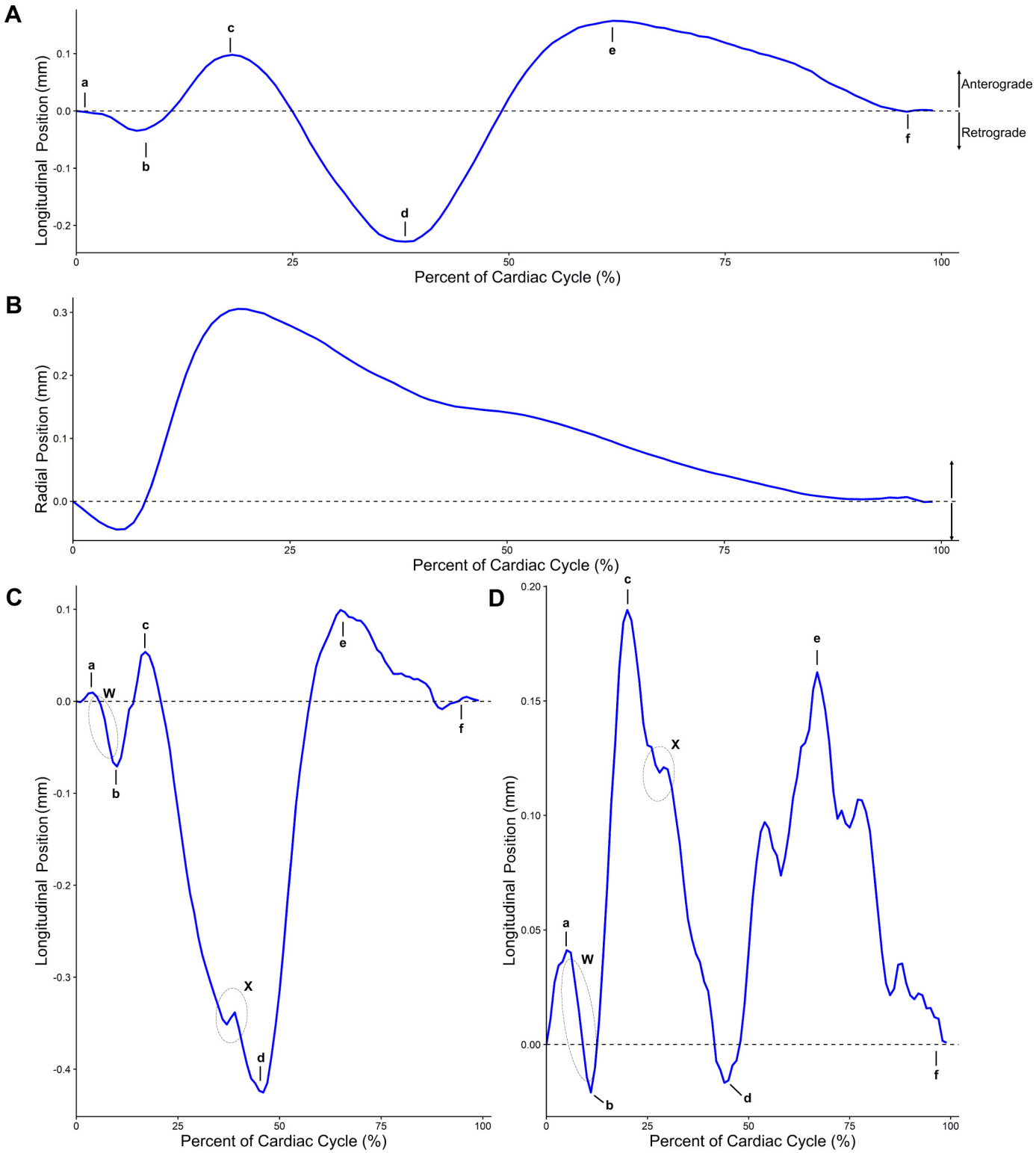

Figure 1. Sample of average ECG-gated longitudinal (*A*) and radial common (*B*) carotid arterial wall motion from a sample of 161 healthy adults (117 males; aged 23 ± 4). Three distinct longitudinal wall motion (LWM) phases can be identified including systolic anterograde LWM (b and c), systolic retrograde LWM (c and d), and diastolic LWM (d and e). Baseline start and end points of the longitudinal trace are shown at a and f, respectively. Individual examples (*C* and *D*) indicate the variability in direction and magnitude of LWM even within apparently healthy individuals. *Phases X* and *W* (dotted circles) have been highlighted for comparison between individuals, and these phases do not appear in group-averaged data. All traces were analyzed with custom speckle tracking software and have been normalized to one cardiac cycle, with bias removed to return the tracking kernel to the reference position by the end of the cardiac cycle. Figure adapted from data collected from Zahnd et al. (12).

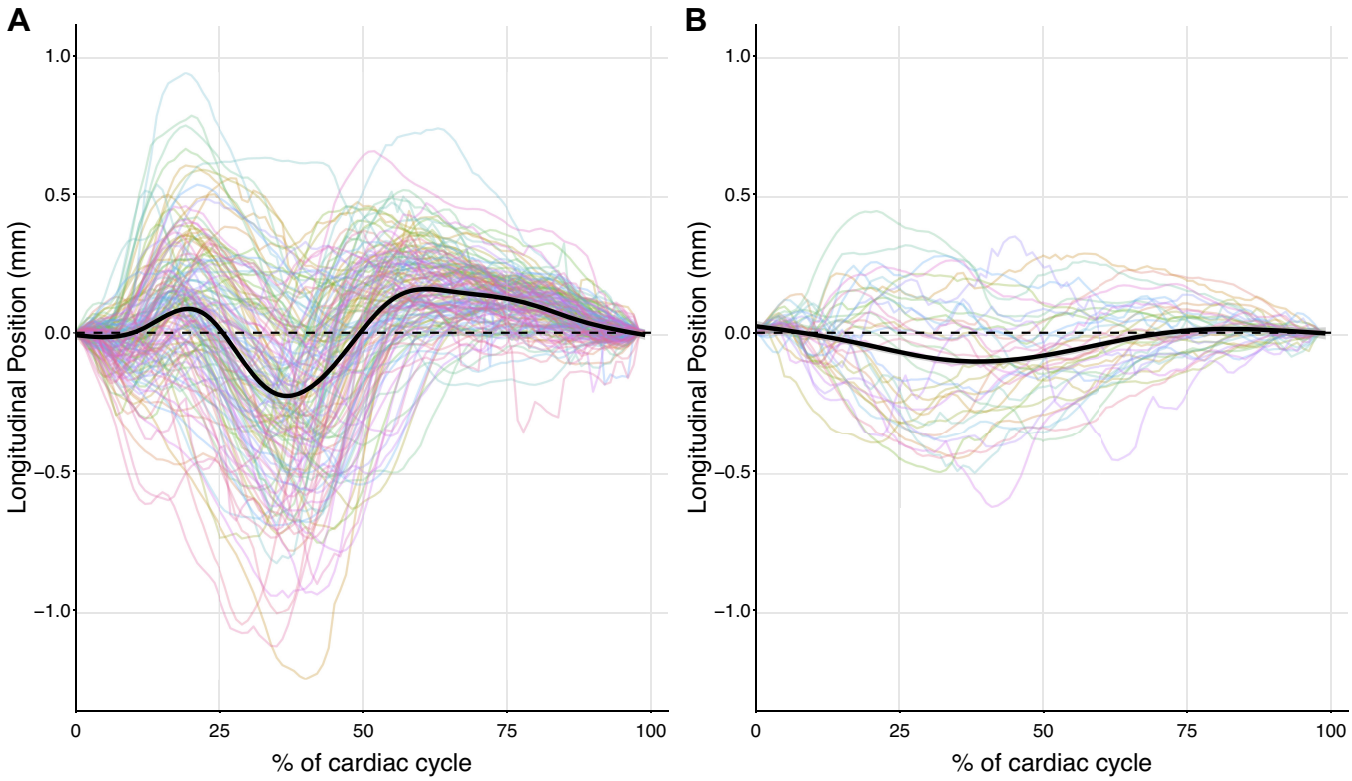

Figure 2. Cycle-normalized, ECG-gated, and bias-adjusted common carotid artery longitudinal motion traces from 161 younger healthy adults (117 males; aged 23 ± 4; *A*) and 51 older healthy adults (30 males; aged 69 ± 6; *B*). Colored lines indicate individual traces, whereas the solid black line represents the group averaged trace. There is a large amount of variability between individuals regarding the amplitude and duration of each motion phase as well as age-related changes resulting in a diminished LWM amplitude in the older healthy adults. Despite the variability, the general anterograde-retrograde shape of the pattern remains consistent. LWM, longitudinal wall motion. Figure adapted from data collected from Zahnd et al. (12).

in recorded strain angles may be due to the use of estimation methods rather than direct measures. Consistent reports of intramural shear strain (9, 11, 15, 28, 32, 33) have made it one of the hallmark features of LWM.

Intramural shear strain has the potential to provide an indication of intramural elasticity, reflecting properties of the connecting tissues between the distinct wall layers. Of note, the external elastic lamina separates the adventitial and medial wall layers and may be one such structure under direct tension through LWM-induced intramural shear strain. The external elastic lamina may also be exposed to repetitive strain damage over the lifespan (34), contributing to the gradual shift to a stiffer vascular phenotype commonly described in the vascular aging process (35). Although the measurement of intramural strain is promising to examine the arterial wall through a new lens, there is scarce research on this topic and additional work is needed to understand how this phenomenon fits into our view of vascular aging and cardiovascular damage in humans.

Progressive Motion Attenuation

LWM is progressively attenuated along the length of an artery such that distal regions with smaller diameters will experience smaller LWM amplitudes compared with those proximal to the heart with larger diameters (12). Cinthio et al. (11) observed regional differences when measuring LWM at the common carotid, abdominal aorta, brachial, and popliteal arteries, generally observing smaller LWM in peripheral compared with central vessels. Progressive attenuation may provide value as a health outcome such that greater attenuation equates to steeper stiffness gradients (12). Suggested explanations for attenuation relate back to the material and structural composition of vessels. Central arteries typically have larger diameters and contain predominantly elastic fibers, whereas peripheral arteries have smaller diameters and contain more vascular smooth muscle cells (VSMCs) (36). This difference in material composition may contribute to the attenuation of LWM, with porcine studies showing a proximal-distal gradient in aortic wall composition and arterial mechanical properties (37). In addition, the decrease in diameter from central to peripheral vessels may also diminish LWM since, in absolute terms, a smaller artery will generally distend less and, hence, will also show a diminished (absolute) LWM through axial-circumferential coupling. However, further research is needed to fully establish the role of such coupling in LWM. The concept of progressive motion attenuation has also led to the notion that central energy sources (i.e., cardiac factors) may contribute to LWM magnitude (11, 38), which will be discussed in depth below.

LWM Differences between Right and Left Common Carotid Arteries

Despite the presence of the brachiocephalic origin of the right common carotid artery on the right side (vs. left common

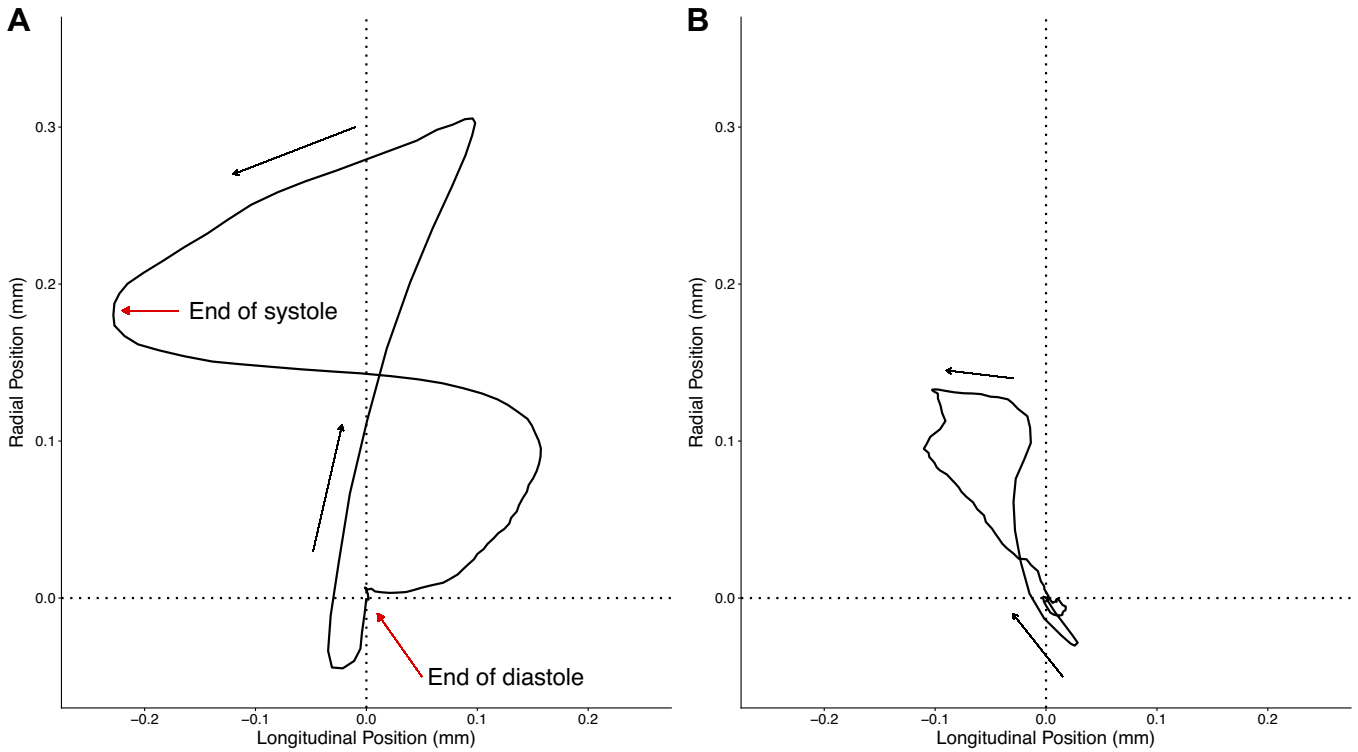

Figure 3. Examples of group-averaged 2-D motion loops, which combine ECG-gated common carotid longitudinal and radial arterial positions. The motion loop provides a visual representation of the suggested radial-longitudinal motion coupling that occurs throughout the cardiac cycle. The general "figure 8" pattern is conserved with motion magnitudes substantially altered between the young (n = 161; 117 males; aged 23 ± 4 yr; *A*) and old (n = 51; 30 males; aged 69 ± 6 yr; *B*) age groups. Figure adapted from data collected from Zahnd et al. (12).

carotid origin on the aortic arch), a preliminary study (n = 10) suggested no between-side differences in LWM at the carotid arteries (39). More recent evidence (n = 93) contests this finding, reporting larger LWM in the left versus right CCA (26). These left-–right discrepancies may be explained by anatomical variations, such as the number of bifurcations and total path length from the aortic arch to the imaging location near the carotid bifurcation (26).

ARTERIAL WALL COMPOSITION AND FIBER ORIENTATION

The above general observations from preliminary LWM studies suggest arterial wall composition plays an important role in dictating longitudinal wall behavior, both at the segment level (i.e., differences among vessels), as well as within a specific region (i.e., intramural strain). This is not surprising given the clear role of extracellular content in determining regional variation in conventional measures of arterial stiffness and input impedance. Here, we review the composition of arterial wall layers (specifically in elastic arteries) and the theorized impact of fiber orientation differences on LWM.

Composition of Arterial Wall Layers

The tunica intima is composed of the endothelium, basal membrane, and subendothelial layer consisting of smooth muscle and collagen (40). The intimal layer is separated from the tunica media by the internal elastic lamina. The tunica media is where most histological differences are seen between arteries; for example, the CCA is predominantly an elastic artery containing mainly elastic fibers in its media with some VSMCs, whereas the internal carotid artery is a more muscular artery and contains more smooth muscle than elastic fibers. Peripheral arteries also have higher collagen-to-elastin mass ratio (41.9%:17.6%) compared with central arteries (21.5%: 29.8%; percentages given with respect to total arterial wall mass) (41). The media is separated from the tunica adventitia by the external elastic lamina. The adventitial layer is composed of fibroblasts, fibrocytes, ground substance, and collagen fibers (18). Although the external borders of the adventitia are poorly defined, it is known to be surrounded by a loose connective tissue tethering it to the surrounding tissue (42). In addition to distinct compositions, each arterial wall layer has varying orientations of collagen, elastin, and VSMC that are not uniformly arranged. Each extracellular matrix component is oriented in such a way to provide a specific functional purpose to arterial motion and likely contributes to some of the intramural differences observed in LWM. In the remainder of this section, we will discuss the composition and orientations of the tunica media and adventitia and how they might relate to LWM. The intimal layer will not be reviewed in depth since it contains minimal amounts of smooth muscle and collagen resulting in a thin layer that provides negligible mechanical strength in young healthy arteries (19).

Tunica Media

The tunica media is the predominant layer for VSMC, which have been generally identified as circumferentially

oriented using polarized light microscopy. Canham et al. (43) used a polarizing microscope with a four-axis stage to determine pressure dependence of orientations in fixated human coronary arteries. They indicated that medial VSMC show a circumferential orientation, which allows for strength in the circumferential direction when high loads are placed upon the wall (18). There may be a direct role of VSMC mechanics on intima media function (44), although the impact on LWM requires further study. Medial collagen and elastin maintain a unique fiber orientation estimated as a gradient of axial to circumferential orientation from deep to superficial (Fig. 4). Timmins et al. (45) examined medial collagen and elastin fibers in bovine common carotid arteries using a nonlinear optical microscope allowing for visualization of the distribution and orientation of wall tissues. Both collagen and elastin toward the intima maintained an axial orientation, whereas fibers closer to the adventitia appeared to be circumferentially arranged (45). The authors hypothesized that axial and circumferential orientations are a result of the stresses experienced in those areas (i.e., "form follows function") with axial shear stress forces resulting in more axially oriented fibers nearest the innermost regions and compressive circumferential stress from cyclic pulse pressure waves causing more circumferential fibers in the outer regions of the media (45). However, circumferential stress is uniform throughout the arterial wall in developed vessels (46) with constant longitudinal tension, and the relative importance of fiber orientation versus wall tension in determining LWM in vivo, hence, requires further research.

As a competing recent theory, collagen fibers have also been described as having variability in small-pitch helical formations (47, 48). At a basic mechanical level, crossing helical orientations allow relatively constant axial forces over a range of physiological distending pressures. With pressure-induced distension, a radial force is exerted throughout the arterial wall, causing contained fibers and cells to reorganize and elongate within the wall in the axial-circumferential plane (49). However, there is likely not one single helical "bundle" within the wall that directly leads to axial-circumferential coupling. Arteries are often described as having two symmetric families of helical fibers at opposing angles, creating an interlocking pattern that minimizes fluctuations in longitudinal force and hence minimizes longitudinal motion (50). This structurally integral component of the arterial wall brings to light a potential mechanical consideration with 2-D wall coupling patterns, although there may not be a direct association between helical orientations and LWM.

Tunica Adventitia

As opposed to medial fiber orientations, there is poor consensus on whether the adventitial collagen fibers are circumferentially (43, 51) or longitudinally oriented (42, 52, 53). Polarized light microscopy has shown high concentrations of collagen fibers arranged in a circumferential formation though with a more dispersed array of data points as compared with medial smooth muscle (inclination angle standard deviation of 22.2° vs. 4.2°) (43). Increased dispersion indicates varying collagen orientations throughout the adventitia, which would explain both circumferential and longitudinal arrangements being reported (43, 53). The varying orientations may also be due to obscurities caused by the wavy nature of adventitial collagen fibers. Chow et al. (54) detected circumferential and longitudinal orientations of

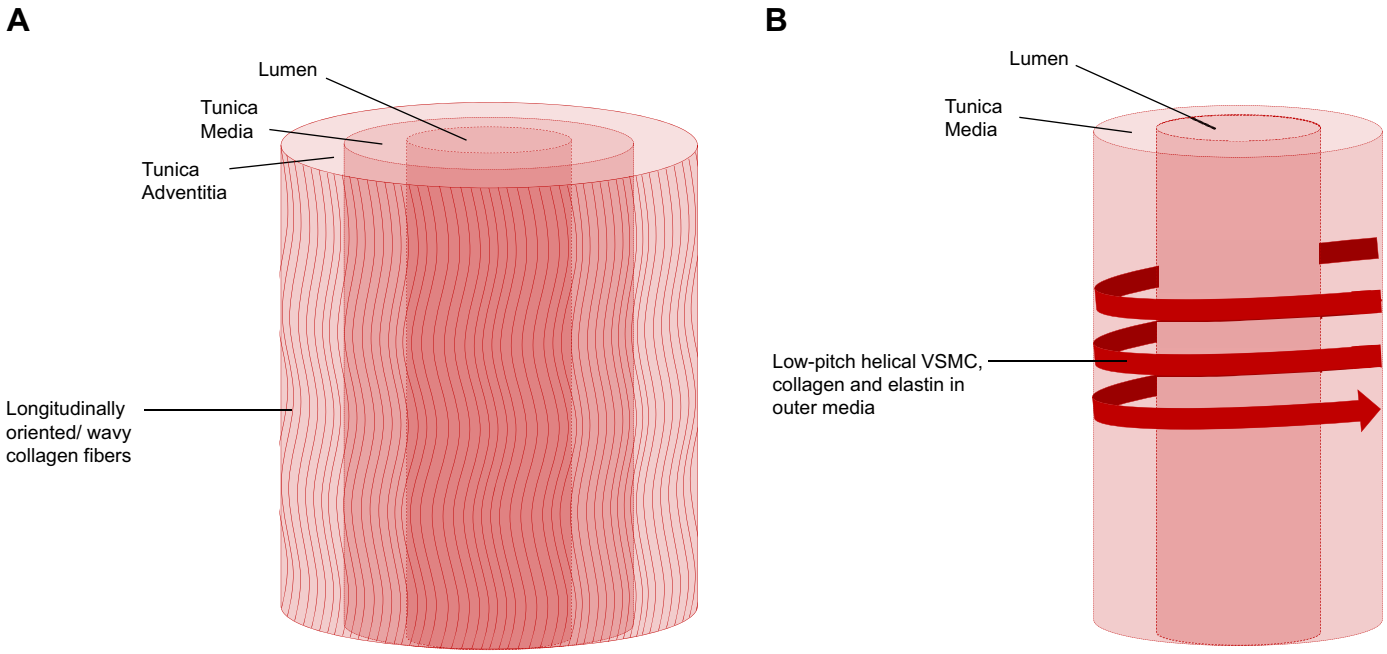

Figure 4. Schematic of theorized orientations of adventitial (*A*) and medial (*B*) arterial wall layers. Adventitial collagen fibers are depicted as longitudinally oriented wavy structures. Medial fibers can be described as circumferentially oriented with a low pitch, functionally acting as a helical arrangement. The variation in fiber orientation throughout the arterial wall layers directly relate to their unique functions contributing to longitudinal and circumferential motion.

adventitial collagen fibers, attributing variability to differences in mechanical load and obscurities at low strain due to wavy fibers. The ratio of circumferential to longitudinal collagen fibers favored circumferential orientations when undergoing circumferential strain and longitudinal arrangement under longitudinal strain, whereas nonexistent or minimal mechanical loading led to more evident circumferential fibers, supporting a slightly more dominant circumferential conformation (54). Taken together, adventitial collagen orientation seems to *1*) be concentrated around two oblique average orientations (with orientations in between circumferential and longitudinal, though presumably slightly more circumferential), but *2*) with considerable dispersion around these average orientations. The oblique average orientations presumably reduce adventitial wall motion through reduction of longitudinal force fluctuations with pressure fluctuations. Reduced adventitial wall motion is likely further compounded by arterial tethering of the adventitia to the surrounding tissue, resulting in the motion gradient used to determine intramural strain (11).

In summary, it is conceivable that fiber orientation-based differences between wall layers could contribute to differences in LWM between layers, and partly explain coupling of radial and longitudinal wall motion observed in 2-D motion loops (Fig. 3), and timing of specific LWM phases during the dicrotic notch and *phase X* (25).

LONGITUDINAL PRESTRETCH

In situ, arteries are naturally stretched, resulting in a basal level of longitudinal strain and tension within the wall. This is immediately apparent during arterial excision, where the ex situ length is significantly reduced due to retractive forces retracting the vessel, akin to a loose elastic band (55). The ratio of in situ-to-ex situ length is known as longitudinal prestretch (LPS) (17). One of the first documented cases of LPS comes from Fuchs (55) and has been consistently reproduced (56–58), specifically in animals and postmortem human examinations due to the invasive nature of the procedure. Dobrin et al. (56) investigated the effects of elastase and collagenase on LPS in human cadaveric arteries to determine the main extracellular contributions to retraction. Elastase treatment resulted in decreased longitudinal force (less retraction) whereas collagenase caused minimal force reductions, suggesting elastin is the main functional element for LPS. Age-related changes in LPS further support the importance of elastin in longitudinal tension (59) as there are parallel age-related reductions in elastin, which are already known to contribute to arterial stiffening across the lifespan (60). Rough estimates suggest that in the human abdominal aorta, LPS decreases from ~1.30 (30% strain) at age 20–30 yr to 1.095 (9.5% strain) at age 60–70 yr (61), matching relative changes in elastin across the same timespan (62% decrease in amount of elastin from age 14–90) (62).

LPS is functionally important because of the intrinsic, fundamental coupling between longitudinal and circumferential arterial mechanics (63). This coupling implies that circumferential deformations (e.g., caused by radial distension) will not only influence circumferential, but also longitudinal wall stress. Such coupling, hence, may be of vital importance in the context of LWM. Despite this intrinsic coupling, arteries have evolved to possess a curious property: when stretched to their LPS (sometimes called in vivo axial stretch), an increase in pressure typically leads to only a small change in longitudinal force (64). When the vessel is stretched longitudinally beyond its LPS, a pressure increase leads to a force increase; when stretched below the LPS, a pressure increase leads to a force decrease. If this force decrease is of such magnitude that force becomes negative (i.e., compressive instead of tensile), the artery will start to buckle, potentially resulting in arterial tortuosity (56). Tortuosity can result in altered shear stress and plaque development due to local variations in arterial bends and curves along a segment (65, 66). The inversion point of the pressure-longitudinal force relationship is often used in laboratory studies to estimate an artery's in vivo LPS without having to actually measure the amount of retraction when the artery is excised (61). We will term the corresponding LPS the inversion LPS (LPS_{inv}). Besides buckling prevention, due to longitudinal-circumferential coupling, LPS ensures that circumferentially, the artery is at a favorable "working point" (17, 61), which may increase distensibility, in turn leading to a larger pressure buffering capacity of the artery (Windkessel effect) and hence limiting pulse pressure and reducing the risk of pressure-induced vascular damage (60).

With respect to LWM, there is a logical role of LPS in modifying the degree of longitudinal displacement. For instance, depending on the true LPS with respect to LPS_{inv}, a pressure increase may lead to an increase, no change, or a decrease in longitudinal force and hence stretch. It is known that with age, LPS and LPS_{inv} decrease (61). However, Horny et al. (61) also showed that the level of actual LPS with respect to LPS_{inv} significantly influenced the longitudinal force and hence longitudinal stretch variation. Taken together, it is conceivable that the degree of longitudinal stretch would directly impact the LWM. Observational data from older adults suggest that both LPS and LWM decrease with age (13, 25, 61), suggesting that as arteries buckle due to a lack of retractive forces, wall layers also have less ability to shift anterograde-retrograde. Although it is highly likely that these observations are mediated by changes in the elastin-to-collagen ratio with age, the exact nature of the relationship between LPS and LWM remains to be elucidated. Given the clear functional role of LPS in maintaining the structure of vessels, there may be untapped value in investigating whether measurement of LWM may be a noninvasive estimate of LPS in living systems.

CURRENT HYPOTHESES ON THE REGULATION ON LONGITUDINAL WALL MOTION

The reproducibility of cross-sectional observations, clinical predictive links, and stability of individual motion patterns refutes the original notion that LWM observations are ultrasonic "noise" (3). Here, we summarize two prevailing theories of why LWM occurs, integrating the above observations to guide future mechanistic work in the area. Notably, these theories are not mutually exclusive, and may each explain separate aspects of the LWM waveform.

Longitudinal-Circumferential Mechanical Coupling

The most logical approach to understanding LWM is to contextualize the patterns with direct reference to pressure-induced distension. Alignment of events around the systolic pressure wave, dicrotic notch, and diastolic creep points toward coupled 2-D wall events throughout the cardiac cycle (Fig. 1). The relationship between radial and longitudinal wall motion is seen in 2-D wall motion loops (Fig. 3), demonstrating temporal consistency in both systolic and diastolic phases in a "figure 8" displacement pattern (21, 67). As described previously, longitudinal-circumferential coupling is fundamental to arterial mechanics and is supported by the presence of loose helical fibers in the artery wall (43, 47, 48, 51, 68, 69) as well as the constant force of LPS through the wall. This paradigm is supported by the notion that 2-D (radial-longitudinal) arterial motion loops preserve their shape (but not their scale) with aging.

As a practical recommendation, the clear relationship between radial and longitudinal wall motion requires more consistent reporting as outcomes in LWM studies. Yli-Ollila et al. (24) initially reported radial-axial wall path length (RAlength) to encapsulate the total displacement of the wall during a cardiac cycle. RAlength appears to be a good global indicator of wall mobility and evidence exists to suggest it reflects arterial stiffness properties (30) and predictably changes with age in healthy children (10). There also may be a direct link between pressure and LWM as shown in studies examining porcine models, finding that with an epinephrine-induced blood pressure increase, longitudinal displacement increased to a greater extent than radial distension (1 mm vs. 0.2 mm) (29). Some questions remain as how best to measure 2-D wall motion; for instance, current analyses predominantly consider a single wall where radial motion may reflect displacement of the entire vessel rather than lumen expansion per se. Simultaneous capture of two-wall vessel expansion and longitudinal displacement is more ideal to study the interplay between radial and longitudinal motion.

Structural Ventricular Vascular Coupling

2-D motion coupling provides an excellent basis for understanding LWM, though it does not explain why there is a distinct retrograde motion phase in which the wall is retracted past its end-diastolic set-point. Moreover, if longitudinal motion would be directly and only related to circumferential motion/stretch, 2-D wall motion loops would have a line or curve shape rather than a loop. A central theory linking energy input to motion output is necessary to understand coordinated longitudinal control of the arterial wall. To account for this observation, Au et al. (70) originally proposed a structural ventricular vascular coupling effect wherein anterograde wall motion is influenced by local blood velocity (i.e., pushing force) and retrograde wall motion is influenced by cardiac motion (i.e., pulling force), whereas the absolute wall displacements and wall velocities are influenced by the material stiffness of the vessel (70). This theory was motivated by simultaneous observations between local blood velocity, cardiac motion, and LWM and accounts for the large degree of pattern variability observed between otherwise healthy adults (Fig. 2). Further in vivo experiments through case studies (71), acute experimental designs (9, 28, 38), and chronic lifestyle interventions (10, 72) have expanded on this structural coupling theory, necessitating revision of this theory, which we update in this review.

Anterograde wall motion.

Originally, Au et al. (70) hypothesized that anterograde LWM was associated with local blood velocity through a physical shearing effect of blood on the vessel wall. This remains an unsupported hypothesis with available evidence pointing toward a negligible, if any, effect of local shear stress on anterograde wall motion. In fact, anterograde wall motion has proven difficult to manipulate in general, without clear changes in response to acute experimental designs with $+20$ mmHg shifts in mean arterial pressure (38), and spontaneous recordings during premature ventricular contractions that abolish the forward blood velocity wave (71). Experiments in pigs have also suggested LWM is more strongly influenced by distending pressure as opposed to blood velocity (28). Au et al. and others (28, 73) have discussed that the order of magnitude of wall shear stress may be too small to meaningfully impact the arterial wall, though there have so far been no mathematical proofs for the longitudinal shearing force. To further this discussion, we now present a first-order estimate of the wall shear stress-induced longitudinal force, stretch and displacement in the human common carotid artery. Assuming an in vivo carotid artery length of l = 13 cm and inner diameter of d = 8 mm (74), the total inner surface is:

$$A = \pi dl = 3.3 \cdot 10^{-3}\ \mathrm{m}^2$$

We assume a peak carotid wall shear stress of $\tau = 2$ Pa based on reported peak carotid wall shear stress values from 0.7 to 3.5 Pa (75, 76), which leads to a total shear force of:

$$\mathrm{F}_\tau = \tau A = 6.5\ \mathrm{mN}$$

The axial force associated with longitudinal prestretch for a human common carotid artery is taken to be F_{LPS} = 0.43 N (4). On top of F_{LPS}, shear stress could induce a 1.5% force modulation. To estimate the potential influence of such force modulation on longitudinal stretch, we used force-length data measured in dog carotid arteries (Fig. 5) (77). Accordingly, at a pressure of 120 mmHg, force is 0.245 N and the length-force slope $\mathrm{d}l/\mathrm{dF} = 1.41$ cm/N. Hence, a force modulation of 1.5% would lead to a length fluctuation of $0.245\ \mathrm{N} \cdot 1.41\ \mathrm{cm/N} \cdot \frac{1.5\%}{100\%} = 0.053$ mm, with respect to a reported in vivo length of 4.5 cm (i.e., a length fluctuation of 0.12% with respect to in vivo length). For our assumed human carotid in vivo length l of 13 cm, 0.12% would amount to a (shear stress-induced) length fluctuation of 0.15 mm. Taken together, even with a modulation of the estimated shear stress by ±2 Pa, this fluctuation is on the same order of magnitude as reported on anterograde LWM values. Although these estimations do support a theoretical role of shear stress impacting anterograde LWM, we assumed an untethered common carotid segment as a perfect cylinder, with a single estimate of shear stress—tethering would reduce the calculated LWM herein. Nilsson et al. (78), however, found that if the longitudinal elastic modulus of the inner layers of the arterial wall was calculated based only on

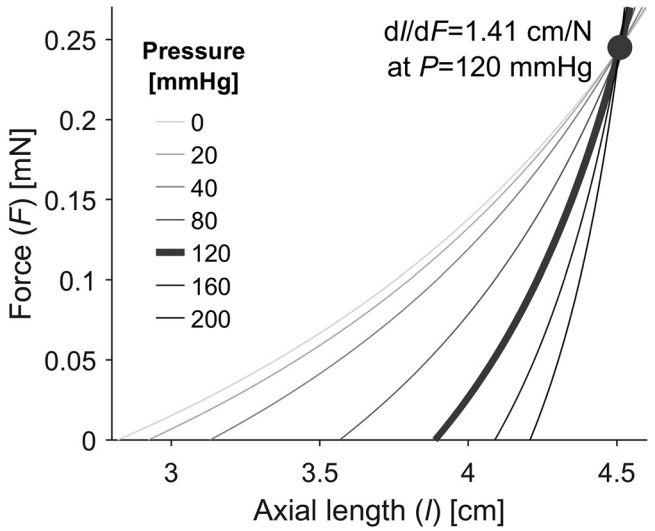

Figure 5. Relationship between axial force and length in dog carotid arteries, at different values of luminal pressures. At the crossover point (corresponding to the in vivo axial length), the tangent was determined for the 120 mmHg curve. Figure recreated based on data from Van Loon et al. (77). Used with permission.

shear stress as the driving force, its value would be ~1000 times lower than anticipated from ex vivo experiments, suggesting that driving factors other than shear stress may be at play. In line with this, Stevens and Au (71) recently reported a unique case study during spontaneous premature ventricular contractions, wherein anterograde LWM did not change even with a ~80 cm/s change in peak blood velocity (71), indicating that in practice shear stress may only have a small impact on LWM, and that other hemodynamic factors (e.g., distending pressure, arterial stiffness, cardiac confounders) may have a larger impact on LWM.

Despite the minimal magnitude of shear forces, wall shear stress may contribute to some extent to carotid LWM. There may be other competing influences that have introduced uncertainty to in vivo measurements, such as 2-D radial-axial motion coupling. This theory is difficult to support in vivo and experiments in isolated arteries are likely required. Regardless, available clinical evidence does not support a central role of anterograde wall motion in cardiovascular risk prediction or health outcomes (15), implicating the anterograde phase as a small component of the larger LWM pattern.

Retrograde wall motion.

There is greater support for the link between retrograde wall displacement and cardiac motion. Originally proposed by Cinthio et al. (11), there are a few key observations that implicate a central energy source actively "pulling" the arterial wall: *1*) the magnitude of retrograde displacement is often larger than the preceding anterograde displacement, suggesting it is not a passive event; *2*) progressive motion attenuation distal to the heart suggests there is a loss of energy further from a motion source (12), with peripheral arteries (i.e., brachial and femoral arteries) exhibiting little-to-no LWM; and *3*) motion between the left and right carotid arteries differs, as does the bilateral path length from the left/right carotids and the aortic arch (26). Taken together, there is adequate rationale to support a major role for a central energy source in driving the motion. We hypothesize that as the left ventricle contracts, the fibrous aortic annulus descends to pull down the proximal vasculature (Fig. 6); Au et al. (70) have provided timing evidence that these events are temporally linked, with maximum left ventricular action occurring just before the carotid artery reaching its maximal retrograde position (70). There is less evidence for a magnitude-based relationship as it is difficult to drastically alter cardiac mechanics in vivo, though our past experimental work points toward a moderate influence of cardiac mechanics impacting carotid LWM through pressor interventions (38) and arrhythmias (71). Further investigations on the role of cardiac mechanics on arterial function should focus on ex vivo or postmortem cadaver models, as the main criticism of this work is the difficulty in isolating regulatory factors such as pressure, flow, and cardiac function; in healthy systems, these features are implicitly linked and cannot be easily changed without impacting another outcome.

Wall stiffness.

Finally, the role of arterial stiffness should be considered in the interpretation of LWM patterns. LPS likely has a major role in determining the propensity for LWM in living systems. In healthy, young arteries, a strong retraction force keeps arteries "taut," with elastin reorganizing to accommodate changes in arterial length with age (17). In this situation, arteries are quite mobile and may displace proportionate to an energy source (i.e., left ventricle), while tethered to an end point (i.e., downstream branches fixed in tissues as the microvasculature). As individuals age and arteries stiffen, there is a gradual shift in LPS, where elastin degradation and collagen redeposition reduce the internal retraction forces, eventually leading to arterial tortuosity (56). Accumulation of connective tissue surrounding arteries also increases local tethering, additionally preventing excessive LWM. Under this view, the magnitude of LWM is an indirect measure of prestretch, which agrees with the available clinical cross-sectional studies linking total motion with conventional markers of arterial stiffness such as carotid-femoral pulse wave velocity and local arterial compliance (13, 23, 25, 79). Although it is clear that LWM is linked to arterial stiffness, the relationship between specific motion properties to material stiffness elements remains to be examined, which may also shed light on whether "longitudinal stiffness" is distinct from conventional radial stiffness and therefore offers independent predictive benefit for cardiovascular risk and healthy vascular aging.

Governing equations.

In response to the available human physiological data, Hao et al. (80) have recently proposed a series of preliminary mathematical governing equations that relate longitudinal motion to local elasticity, shear stress, and cardiac energy input. Their model [building upon their previous model in Choudhry et al.(74)] is formulated as a boundary-value problem of nonhomogeneous wave propagation in a semiinfinite domain; in brief, it describes how a longitudinal elastic wave propagates through the proximal vasculature in response to energy input from cardiac mechanics, which is subsequently modified by ascending aortic elasticity (represented as

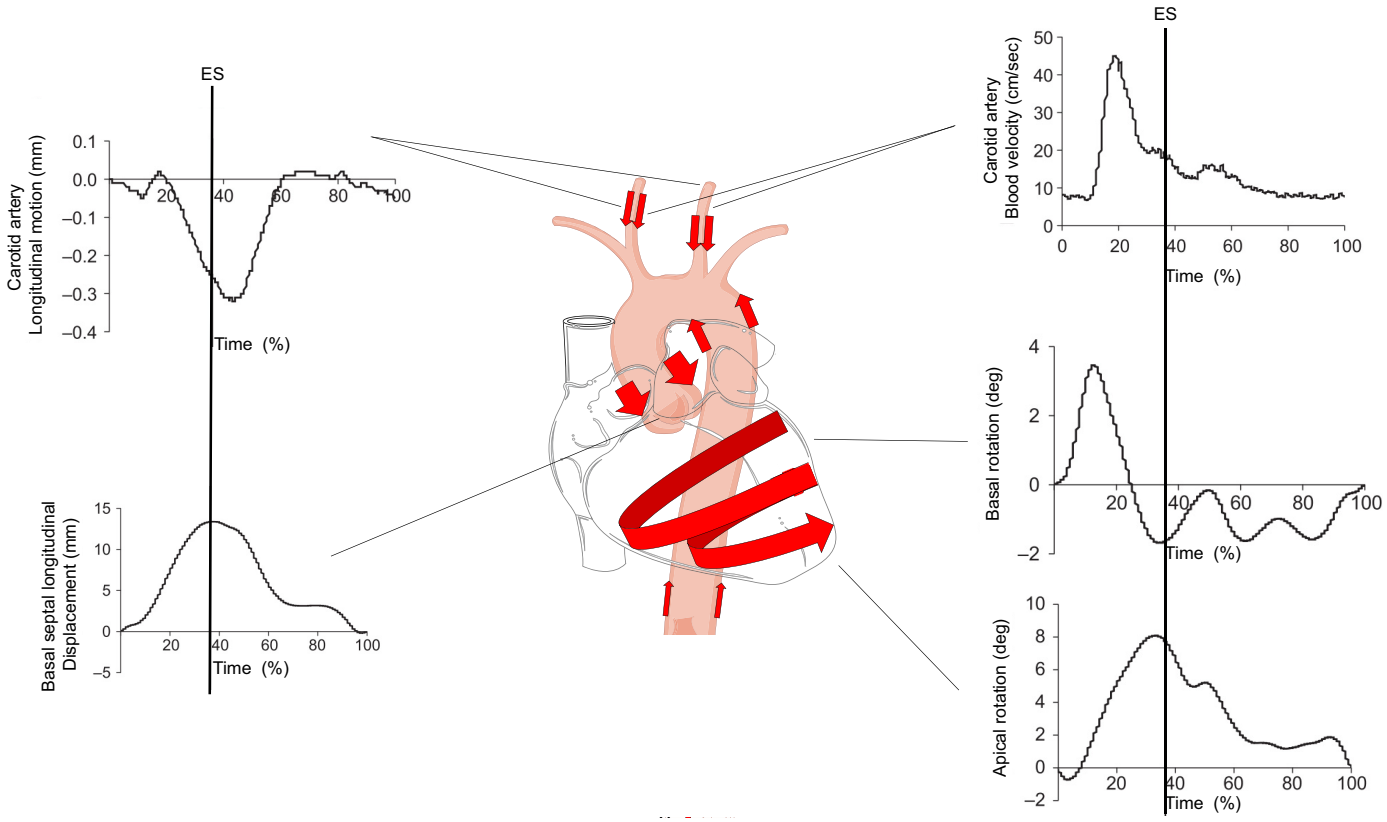

Figure 6. Schematic hypothesizing a structural ventricular vascular coupling effect between the left ventricle and the proximal vasculature. As the heart contracts, the aortic ring and proximal aorta will pull the vascular wall toward the heart. The magnitude of motion will dissipate with increasing distance from the left ventricle with the most distal portions experiencing the least amount of motion. ES, end-systole. Components of figure adapted from Au et al. (70).

longitudinal prestretch), carotid shear stress, and carotid elasticity. This mechanistic model serves as a starting point for LWM modeling at the carotid artery, expressing ecological validity with respect to the few available studies that provide human physiological data (9, 28, 38, 70). Some limitations are noted, including reliance on basal rotation of the left ventricle as the primary energy source, simplification of longitudinal prestretch considerations, and neglect of radial wall motion in the control model. Basal rotation of the left ventricle appears to be a satisfactory representation of cardiac movement (38), though a more accurate measure may be longitudinal displacement of the aortic annulus connective tissue as a direct assessment of energy input into the vascular system. Longitudinal prestretch of the ascending aorta is a key component of longitudinal energy transfer, though as noted above, this is impossible to measure in vivo and is therefore difficult to identify its exact role in the control system. Finally, given the helical orientation of medial fibers at the carotid artery (47, 48), longitudinal-circumferential coupling likely plays a larger role than hypothesized in controlling LWM, though this relationship remains understudied. Additional ex vivo validation and simulation studies are required to further tune these theoretical equations and compare with physiological data. Previous simulation studies on LWM exist in the literature (16, 31, 35, 75). These studies may offer valuable information regarding LWM; however, these studies are limited by *1*) the absence of in vivo data, making it difficult to evaluate their accuracy or validity in integrative physiological systems and *2*) the use of isotropic arterial wall models, which do not capture the physiological relationship between longitudinal prestretch and pressure.

In summary, the best available evidence points toward a combination of 2-D radial-axial wall coupling and ventricular vascular coupling as an initially valid hypothesis for the origins of LWM. Many key questions are left unanswered in this paradigm, making it a ripe field for discovery in vascular physiology. The availability of vascular ultrasound measurement and open-source analysis programs has contributed to an accessible point-of-entry for physiologists interested in this field (15). Interdisciplinary collaboration will be key for further advances in discovery, testing the above hypotheses through simulation, histological, and translational approaches.

CONCLUSIONS

LWM is a reproducible observation and can be directly linked to known features of arterial wall physiology. Key observations from LWM studies in humans point toward a regulatory system rather than random noise; these include oscillatory longitudinal displacement around a set-point, temporal 2-D coupling between radial and longitudinal displacements, progressive attenuation of LWM along the

length of an arterial segment, as well as intramural strain between layers of the arterial wall. After examining key features of the composition and stresses within the arterial wall, we present an up-to-date summary of current hypotheses on the physiological bases for LWM. Given the continuous helical and circumferential nature of media and adventitial wall layers, there is likely some role of 2-D motion coupling suggesting interdependence of both radial and longitudinal displacements of the wall; we recommend that future studies regularly report 2-D motion loops to account for this interdependence. Substantial retrograde wall motion points toward a central energy source pulling the wall toward the central vasculature, which we outline as a structural ventricular vascular coupling effect. As competing forces are simultaneously in effect, ex vivo or simulation studies are now required to further probe the independent regulation of motion. Available clinical evidence suggests that LWM is an independent predictor of cardiovascular morbidity and further mechanistic investigations are required at the extracellular level to place LWM in the proper context within vascular biology to advance our understanding of longitudinal wall behavior.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

C.E.A. and J.S.A. conceived and designed research; C.E.A., B.S., and J.S.A. prepared figures; C.E.A., B.S., and J.S.A. drafted manuscript; C.E.A., B.S., and J.S.A. edited and revised manuscript; C.E.A., B.S., and J.S.A. approved final version of manuscript.

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