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Abstract—Examining left ventricular midwall as opposed to endocardial mechanics enhances understanding of left ventricular function in individuals with abnormal cardiac geometry. Accordingly, we used carotid ultrasound and applanation tonometry of arterial pressure to derive carotid midwall strain and its relation to carotid peak-systolic and end-diastolic stresses in 82 apparently normal, employed subjects (56 men, 26 women; median age, 47 years; 70% white; 21% overweight) with no evidence of coronary or valvular heart disease. Regression equations relating carotid luminal and midwall strain to the increment in carotid stress during systole (Δcarotid stress) were used to predict strain for the observed Δstress. Observed/predicted carotid luminal or midwall strain was calculated as a measure of carotid luminal or midwall strain for imposed stress, termed stress-corrected strain. Midwall carotid strain was similar in women and men but was negatively related to older age ($r=-0.35$, $P=0.001$) and higher body mass index ($r=-0.31$, $P=0.005$) and brachial and carotid blood pressure ($r=-0.30$ to -0.45, all $P<0.01$). The pulsatile change in arterial load, measured by Δcarotid stress, was positively related to midwall strain ($r=0.44$, $P<0.001$) more closely than was carotid luminal strain. Regression analyses revealed that carotid midwall strain was positively related to Δstress, with additional negative relations to age and carotid diastolic diameter (all $P<0.001$). Stress-corrected carotid midwall strain was strongly and negatively correlated with midwall elastic modulus and Young's modulus (both $r=-0.77$, $P<0.001$), followed by elastic modulus ($r=-0.74$, $P<0.001$), midwall Young's modulus ($r=-0.73$, $P<0.001$), midwall stiffness index ($r=-0.70$, $P<0.001$), and stiffness index ($r=-0.66$, $P<0.001$). Thus, in normal adults, carotid midwall strain is unrelated to gender, is positively related to pulsatile carotid load as measured by Δcarotid stress, and is negatively related to age, overweight, and standard measures of arterial stiffness. (*Hypertension*. 1999;33:787-792.)

Key Words: carotid arteries ■ compliance, arterial ■ ultrasonography

Measurement of arterial compliance may provide indices of early vascular changes that antedate the development of major atherosclerotic disease.[1,2] It is well known that risk factors for vascular disease, including older age, high blood pressure and cholesterol, diabetes, and the presence of left ventricular (LV) hypertrophy, are associated with decreased arterial compliance.[3–15] Thus, noninvasive assessment of arterial compliance may be important for early detection and subsequent prevention of atherosclerotic disease. Several methods to assess arterial compliance noninvasively rely on the relation between systolic strain (lengthening) of the arterial lumen diameter in relation to the pulsatile blood pressure increase.[2,16,17] However, conventional approaches do not examine the average strain of the arterial wall, approximated by lengthening at the arterial midwall, nor do they directly take into account the average stress on the arterial wall. Recent research on the left ventricle reveals that a change of approach to examination of LV midwall mechanics improves understanding of ventricular function in individuals with abnormal cardiac geometry.[18–22] Therefore, the present study was undertaken to assess the level and correlates of the carotid midwall strain-stress relation in apparently normal adults.

Methods

Subjects

The study group consisted of 82 apparently normal men and women drawn from a large employed population in New York.[13,23] All subjects had normal blood pressure (<140/90 mm Hg) on no antihypertensive medication. Segmental wall motion abnormalities and valvular regurgitation or stenosis were excluded by 2-dimensional and Doppler echocardiography. On the basis of the Second National Health and Nutrition Examination Survey (NHANES II), subjects were classified as overweight if they had a body mass index >27.8 kg/m² for men and >27.3 kg/m² for women.[24] Subjects had no clinical evidence of coronary heart disease and gave informed consent under protocols approved in 1979 and regularly thereafter.

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Carotid Ultrasound

A Biosound Genesis II system (OTE Biomedica) equipped with a 7.5-MHz transducer was used to scan the common, internal, and external carotid arteries for discrete carotid plaques.[13,25,26] Two-dimensionally guided M-mode recordings of the common carotid artery ≈ 1 cm proximal to the carotid bulb, with simultaneous ECG and carotid pressure waveforms, were recorded on videotape and subsequently digitized. Electronic calipers were used to measure the internal diameter (D_d) and far wall intimal-medial thickness (IMT_d)[27] at end diastole, at the nadir of the simultaneous arterial pressure waveform, or at minimal arterial diameter, as well as the diameter at peak systole (D_s). All measurements used in this study were performed by a single experienced investigator (M.J.R.) on several cycles and averaged. High interobserver and intraobserver reproducibility for both carotid wall thickness and lumen diameter measurements have been documented.[25,28,29]

Arterial Function Assessment

Arterial pressure waveforms were recorded noninvasively by placing a solid-state high-fidelity external pressure transducer (model SPT-301; Millar Instruments, Inc) over the right common carotid artery while recording M-mode images of the left common carotid artery.[30] Orientation and pressure applied to the transducer were adjusted to applanate the artery between the transducer and underlying tissue, as has been validated to yield accurate estimates of intra-arterial pulse pressure by comparison with simultaneous invasive pressure recordings.[31,32] Actual carotid blood pressures were obtained by external calibration with the use of the mean brachial artery pressure.[25,33,34] An alternative method of calibration that sets both the mean and diastolic carotid pressures equal to those from the brachial artery did not alter the results of the study (data not presented).

Arterial Compliance and Stiffness Indices

Carotid luminal strain, the percent systolic expansion of the arterial lumen,[12] was calculated as

$$\text{Luminal Strain} = ([D_s - D_d]/D_d) \times 100$$

Carotid pressures D_d, D_s, and IMT_d were used to calculate several measures of arterial stiffness, including Peterson's elastic modulus (E_p),[16] Young's elastic modulus (E),[2] and the stiffness index (β),[17,35] using standard formulas. These measures use carotid luminal strain and arterial pressure to provide indices of regional arterial stiffness under the usual loading conditions (E_p) of the vessel or with adjustment for the effects of arterial hypertrophy (E) and distending pressure (β). Systemic arterial compliance was estimated by the ratio stroke volume/brachial pulse pressure[36] and by the arterial compliance index.[37] Cardiac output was calculated from echocardiographic end-diastolic and end-systolic LV volumes.[38]

Measures of Carotid Midwall Function

Carotid midwall strain was derived with the use of a cylindrical model, adapted from Shimizu et al,[18] which assumes that the ratio of volumes of the inner and outer halves of the carotid wall during the cardiac cycle are constant. If it is assumed that the arterial long axis remains constant, inner shell cross-sectional areas at end diastole and at peak systole are equal, as follows:

$$\pi[(D_s/2 + H_s/2)^2 - (D_s/2)^2] = \pi[(D_d/2 + H_d/2)^2 - (D_d/2)^2]$$

where H_s and H_d are the estimated inner shell thicknesses of the carotid walls at peak systole and end diastole, respectively; H_d is considered equal to carotid end-diastolic far wall thickness (FW_d). From the above equation, the systolic thickness of the inner shell and other midwall dimensions can be calculated as follows:

$$\text{Mid}_s = D_s + H_s$$

$$\text{Mid}_d = D_d + FW_d$$

where Mid_d is the midwall diameter in diastole, FW_d is the far wall thickness in diastole, and Mid_s is the midwall diameter in systole.

From these values, carotid midwall strain (expressed as a percentage) is calculated as

$$\text{Midwall Strain} = (\text{Mid}_s - \text{Mid}_d)/\text{Mid}_d \times 100,$$

the midwall Peterson's elastic modulus is calculated as

$$E_{pmid} = [(P_s - P_d)/(\text{Mid}_s - \text{Mid}_d)] \times \text{Mid}_d,$$

and the midwall Young's elastic modulus is calculated as

$$E_{mid} = [(P_s - P_d)/(\text{Mid}_s - \text{Mid}_d)] \times [(\text{Mid}_d)/(FW_d)]$$

The midwall β is calculated as

$$\text{Mid } \beta = [\ln(P_s/P_d)]/[(\text{Mid}_s - \text{Mid}_d)/\text{Mid}_d]$$

Carotid peak-systolic stress (cPSS) was estimated at the midwall from M-mode tracings, adapting a cylindrical model[39] previously used for cardiac studies,[40] in which

$$cPSS = \frac{P_s \times (D_s/2)^2 \times \{1 + [(D_s/2 + H_s/2)^2/(D_s/2 + H_s)^2]\}}{(D_s/2 + H_s)^2 - (D_s/2)^2}$$

Carotid end-diastolic stress (cEDS) was estimated at the midwall by a similar formula. The increment in carotid stress during the cardiac cycle was calculated as

$$\Delta \text{Carotid Stress} = cPSS - cEDS$$

Equations relating carotid luminal strain and carotid midwall strain to Δcarotid stress were then used to predict the expected carotid luminal and midwall strain, respectively, for observed Δcarotid stress. The ratios of observed to predicted strains are termed stress-corrected carotid luminal and midwall strain, respectively.

Statistical Analysis

Data management and analysis were performed with the use of a computer equipped with SPSS 7 (SPSS) software. Data are presented as mean$\pm$SD. Independent sample t tests and ANCOVAs that took into account relevant covariates were used to compare mean values between groups. Pearson correlation coefficients and linear regression analyses were used to determine the closeness and independence of association of variables to midwall strain. The null hypothesis was rejected at $P < 0.05$.

Results

Subject Characteristics

The study population included 56 men and 26 women, with a median age of 50 years. Brachial and carotid artery blood pressures and pulse pressures were virtually identical in the 2 genders. When the population was divided at its median, mean brachial pulse pressure was lower in younger individuals (47 ± 7 versus 54 ± 11 mm Hg, $P = 0.001$) and even more so in the carotid artery (41 ± 11 versus 53 ± 19 mm Hg, $P < 0.001$), as a result of which pulse pressure augmentation from the central to peripheral circulation was greater in younger individuals (6 ± 12 versus 1 ± 17 mm Hg, $P = 0.01$). A total of 17 individuals (11 men) were overweight. Brachial and carotid systolic blood pressures did not differ between weight strata, but both brachial and carotid diastolic blood pressures were higher in overweight individuals (78 ± 6 versus 71 ± 10 mm Hg, $P = 0.004$ and 77 ± 8 versus 68 ± 11 mm Hg, $P = 0.001$, respectively). Most study subjects (79%) were white. No racial differences were observed in any clinical variable.

Relations of Carotid Luminal and Midwall Measures to Clinical Variables

Carotid luminal and midwall systolic and diastolic diameters were larger in men than in women (Table 1), but carotid strain

TABLE 1. Carotid Luminal and Midwall Measurements in Men and Women

Variable	Men (n=56)	Women (n=26)	P
Luminal systolic diameter, mm	6.62±0.66	5.94±0.45	<0.001
Luminal diastolic diameter, mm	5.80±0.64	5.15±0.41	<0.001
Luminal strain, %	14.3±4.3	15.2±3.0	0.327
Midwall systolic diameter, mm	7.24±0.70	6.60±0.57	<0.001
Midwall diastolic diameter, mm	6.50±0.69	5.91±0.54	<0.001
Midwall strain, %	11.6±3.5	11.9±2.3	0.793
Carotid end-systolic stress, 10^3 dyne/cm^2	65.1±15.9	53.8±10.7	0.001
Carotid end-diastolic stress, 10^3 dyne/cm^2	31.0±9.0	23.8±6.0	<0.001
ΔCarotid stress, 10^3 dyne/cm^2	34.1±9.8	30.0±8.0	0.067

did not differ between genders. Men had higher carotid end-systolic and end-diastolic stress than women, but the gender-related difference in Δcarotid stress was not significant. No gender-related differences were observed for other measures of arterial compliance and stiffness (data not shown).

In ANCOVAs, adjusted for gender, neither carotid luminal nor midwall diastolic or systolic diameters or strains differed statistically between overweight and normal-weight individuals (data not presented). However, diastolic and systolic arterial wall thicknesses were higher in overweight individuals (mean, 0.81 versus 0.69 mm, P=0.01 and 0.79 versus 0.65 mm, P=0.003). Carotid peak-systolic stress tended to be lower in overweight individuals (mean, 559 versus 631×10^3 dyne/cm^2, P=0.06), but there was no difference in carotid end-diastolic stress between the groups (mean, 281 versus 289×10^3 dyne/cm^2, P=0.71). As a consequence, the Δcarotid stress was lower in overweight individuals (mean, 278 versus 342×10^3 dyne/cm^2, P=0.01).

Luminal and midwall diameters, arterial wall thicknesses, and luminal and midwall strain were statistically indistinguishable between white and nonwhite individuals. Carotid peak-systolic stress was slightly higher in whites (mean, 631 versus 555×10^3 dyne/cm^2, P=0.05), but carotid end-diastolic stress was similar in the 2 groups. Therefore, Δcarotid stress was higher in whites (mean, 339 versus 285×10^3 dyne/cm^2, P=0.04). Both carotid luminal and midwall strain were

higher in younger individuals (aged <50 years) than in older individuals (15.4±3.6% versus 13.6±4.1%, P=0.04 and 12.7±2.9% versus 10.6±3.0%, P=0.002, respectively).

Univariate analyses (Table 2) revealed that both carotid midwall strain and luminal strain were negatively related to age and body size and that, in general, clinical variables were slightly more closely correlated with carotid midwall strain. In both genders, carotid midwall and luminal strain were negatively related to carotid systolic and diastolic blood pressures but not pulse pressures. In both genders, carotid luminal and midwall strains were negatively related to carotid diastolic diameter (r=−0.49 and −0.39, respectively, both P<0.001). Carotid systolic diameter was not related to either carotid luminal or midwall strain.

Relations of Carotid Luminal Strain and Midwall Strain to Carotid Stress

In men, carotid midwall strain was positively related to Δcarotid stress (r=0.56, P<0.001), while in the smaller group of women this relation (r=0.29) did not attain statistical significance. The overall positive relation between carotid midwall strain and Δstress (r=0.44, P<0.001) is displayed in the top panel of the Figure, with the regression line relating midwall strain to Δstress and its 95% CI. Carotid luminal strain was also positively related to Δcarotid stress in men (r=0.50, P<0.001) but not in women (r=0.15, P=0.45), with a moderate positive relation when men and women were pooled (bottom panel, Figure).

Regression equations relating carotid luminal and midwall strain to Δcarotid stress derived from data in the Figure were used to predict values of the former variables for observed Δcarotid stress. Observed/predicted carotid strain was expressed as a percentage in each individual to yield stress-corrected carotid luminal and midwall strain.
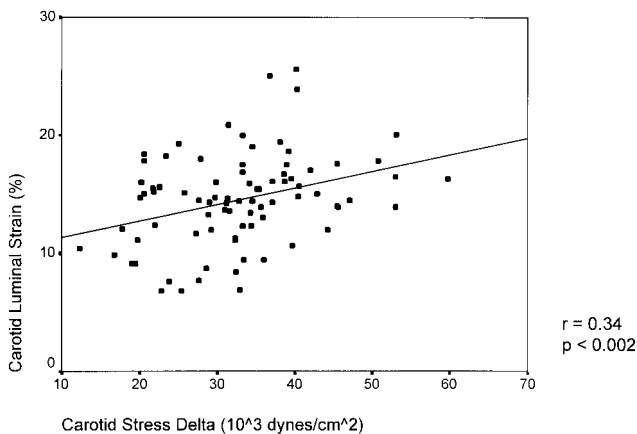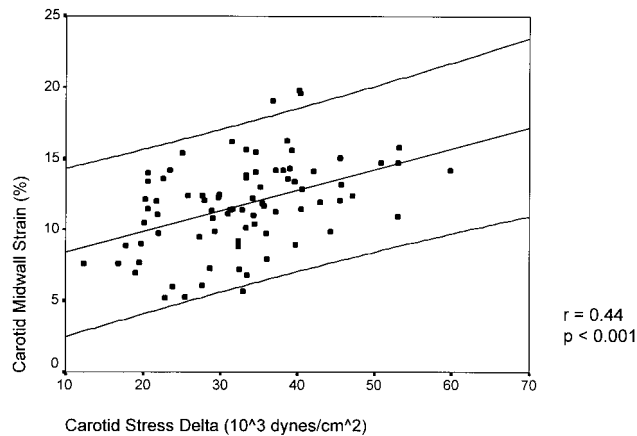
The mean stress-corrected carotid luminal strain tended to be greater for individuals below the median age (104±23%) than for older individuals (94±27%, P=0.08). Stress-corrected luminal strain was lower in men (96±26%) than in women (108±23%, P=0.05). Mean stress-corrected luminal strain was 101±24% in whites and 94±31% in nonwhites (P=0.29). Stress-corrected luminal strain was nearly identical in normal-weight and overweight individuals.

Mean stress-corrected carotid midwall strain was lower in individuals above as opposed to below the median age of the

TABLE 2. Clinical Correlates of Carotid Luminal and Midwall Mechanics

Variable	Luminal Strain	Midwall Strain	Stress-Corrected Luminal Strain	Stress-Corrected Midwall Strain	ΔCarotid Stress
Age	−0.25*	−0.35†	−0.21	−0.31†	−0.13
Body mass index, kg/m^2	−0.26*	−0.31†	−0.16	−0.20	−0.31†
Brachial SBP, mm Hg	−0.24*	−0.30†	−0.22*	−0.29†	−0.07
Brachial DBP, mm Hg	−0.39‡	−0.45‡	−0.33†	−0.37†	−0.24*
Brachial pulse pressure, mm Hg	0.08	0.05	0.04	0.01	0.15
Carotid SBP, mm Hg	−0.22*	−0.30†	−0.29†	−0.41‡	−0.18
Carotid DBP, mm Hg	−0.56‡	−0.33†	−0.18	−0.17	−0.44‡
Carotid pulse pressure, mm Hg	0.013	−0.06	−0.15	−0.29*	0.46‡

*P<0.05; †P<0.01; ‡P<0.001.

Top, Relation of carotid midwall strain to Δcarotid stress. Bottom, Relation of carotid luminal strain to Δcarotid stress.

population (91±25% versus 106±22%, $P=0.007$). Stress-corrected carotid midwall strain tended to be lower in men (96±25%) than in women (105±22%, $P=0.14$). There was no significant difference in stress-corrected carotid midwall strain between races or between overweight and normal-weight individuals. Stress correction of midwall strain

slightly strengthened its negative relations with age and carotid diastolic blood pressure.

Regression Analyses

In a model with carotid luminal strain as the dependent variable and age, carotid diastolic diameter, carotid diastolic blood pressure, and Δcarotid stress as independent variables, carotid luminal strain was related positively to Δcarotid stress ($\beta=0.345$, $P=0.001$) and negatively to carotid diastolic diameter ($\beta=-0.461$, $P<0.001$) and age ($\beta=-0.195$, $P=0.035$) (multiple $R=0.62$). In a similar model, carotid midwall strain was strongly related to Δcarotid stress ($\beta=0.440$, $P<0.001$), age ($\beta=-0.403$, $P=0.001$), and carotid diastolic diameter ($\beta=-0.328$, $P<0.001$) (multiple $R=0.67$).

Relations of Carotid Luminal Strain and Midwall Strain to Other Arterial Compliance Indices

Among the different measures of arterial compliance and stiffness, carotid luminal strain was most closely and negatively related to Peterson's elastic modulus, followed by Young's modulus and β, with a weaker positive relationship with Δcarotid stress (Table 3). Stress-corrected carotid luminal strain was strongly and negatively correlated with Young's modulus, followed by Peterson's elastic modulus and β.

Carotid midwall strain (Table 4) was related to Peterson's elastic modulus, followed by midwall Peterson's modulus, midwall β, β, Young's modulus, midwall Young's modulus, and Δcarotid stress. Stress-corrected midwall strain was strongly and negatively related to midwall Peterson's modulus, followed by Young's modulus, Peterson's modulus, midwall Young's modulus, midwall β, and β. Of note, stress correction of both carotid luminal and midwall strain strengthened their negative relations with all measures of carotid arterial stiffness; the strongest negative relation with each index of arterial stiffness was obtained with stress-corrected midwall strain. Neither the arterial compliance index nor pulse pressure/stroke volume was related to either carotid midwall or luminal strain or stress-corrected strain.

Discussion

Measures of arterial compliance estimate the ability of an artery to expand and contract with cyclic variation in arterial

TABLE 3. Relations of Carotid Luminal Strain and Stress-Corrected Luminal Strain to Stress and Indices of Arterial Compliance

Variable	Luminal Strain		Stress-Corrected Luminal Strain	
	r	P	r	P
ΔCarotid stress, 10^3 dyne/cm^2	0.336	0.002	0.005	0.964
E_p, dyne/cm$^2 \times 10^{-10}$	−0.605	<0.001	−0.683	<0.001
E, dyne/(cm^2 · mm)×10^{-6}	−0.555	<0.001	−0.725	<0.001
β	−0.513	<0.001	−0.587	<0.001
Arterial compliance index, mL/(mm Hg · m^2)	0.025	0.826	0.095	0.401
Stroke volume/pulse pressure, mL/mm Hg	0.060	0.595	0.084	0.455

E indicates Young's elastic modulus; E_p, Peterson's elastic modulus; and β, stiffness index.

TABLE 4. Relations of Carotid Midwall Strain and Stress-Corrected Midwall Strain to Stress and Indices of Arterial Stiffness Compliance

Variable	Midwall Strain		Stress-Corrected Midwall Strain	
	r	P	r	P
ΔCarotid stress, 10^3 dyne/cm^2	0.438	<0.001	0.005	0.962
E_p dyne/cm$^2 \times 10^{-10}$	-0.648	<0.001	-0.738	<0.001
E_{pmid}, dyne/cm$^2 \times 10^{-10}$	-0.640	<0.001	-0.774	<0.001
E, dyne/(cm$^2 \cdot$ mm)$\times 10^{-6}$	-0.530	<0.001	-0.773	<0.001
E_{mid}, dyne/(cm$^2 \cdot$ mm)$\times 10^{-6}$	-0.488	<0.001	-0.734	<0.001
β	-0.550	<0.001	-0.662	<0.001
Mid β	-0.590	<0.001	-0.698	<0.001
Arterial compliance index, mL/(mm Hg $\cdot$ m^2)	0.065	0.562	0.165	0.140
Stroke volume/pulse pressure, mL/mm Hg	0.090	0.421	0.125	0.261

E_p indicates Peterson's elastic modulus; E_{pmid}, midwall Peterson's modulus; E, Young's elastic modulus; E_{mid}, midwall Young's modulus; β, stiffness index; and mid β, midwall stiffness index.

pressures caused by cardiac contraction and relaxation. The most robust noninvasive method to measure in vivo arterial thickness and strain is ultrasound imaging.[4,41,42] The introduction of carotid artery applanation by high-fidelity tonometer has provided a method that, in the hands of highly skilled operators, can provide the central arterial pressure measurements needed for noninvasive calculation of measures of arterial compliance.[31,32] The most commonly used compliance measurement is Peterson's elastic modulus, defined as the ratio of stress (pulse pressure) to strain (lengthening).[16] Under usual loading conditions, a higher stress-strain elastic modulus represents greater arterial stiffness.[16] Young's modulus was derived to adjust for the effect of arterial wall thickening on arterial stiffness.[2] To reduce the impact of the curvilinear pressure-stiffness relationship on arterial stiffness, the stiffness index (β) was developed.[17,35] In one study, β correlated well with the presence of atherosclerosis in pathological findings.[43]

However, conventional approaches do not examine the average strain of the arterial wall, approximated by systolic lengthening at the arterial midwall, nor do they directly take into account the average imposed stress.[44] Thus, examining the average systolic strain of the arterial wall, approximated by measurements at the midwall, and relating it to the average imposed stress may enhance detection of reduced arterial compliance compared with conventional methods.

Although we found no gender-related difference in either carotid luminal or midwall strain, apparently normal men had higher carotid wall stresses than women. The greater stress on the arterial wall in men may be a hitherto unrecognized but pathophysiologically important mechanism contributing to the well-known gender-related difference in risk of arterial disease. In our study, carotid pulse pressure showed a greater increase with age than brachial blood pressure. The loss with age of pulse pressure amplification from central to peripheral

arteries has been attributed to age-related degeneration of arterial elastic fibers.[45]

Our study demonstrates that midwall strain had a stronger negative relation to age than did carotid luminal strain. As expected from physiological considerations, adjustment of carotid luminal and midwall strain for the imposed cyclic load strengthened the negative relations with age. The reason for decreased carotid strain with age may be an age-related progressive shift in load bearing during systole from flexible elastic fibers to rigid collagen fibers that accompanies age-associated arterial dilatation.[45] Our study showed that stress-corrected carotid midwall strain was significantly lower in older individuals, with a parallel trend for stress-corrected luminal strain. Thus, the present findings suggest that the average mechanics of the several components of the carotid artery wall may be better approximated by calculating arterial strain and adjusting it for the pulsatile increase in arterial load (Δcarotid stress) at the level of the arterial midwall. Further study will be needed to determine whether similar negative relations between age and midwall mechanics are also observed in peripheral arteries.

The present study confirmed the expected negative relations between conventional measures of arterial stiffness and parameters of carotid luminal and midwall mechanics. A new and notable result of the present study is that the coefficient of determination (r^2) between standard arterial stiffness measures and measures of arterial mechanics increased stepwise from those observed with carotid luminal strain ($r^2 = 0.26$ to 0.37) to those with stress-corrected midwall strain ($r^2 = 0.44$ to 0.59).

Conclusion

In normal adults, carotid midwall strain is unrelated to gender, positively related to pulsatile carotid load, as measured by Δcarotid stress, and negatively related to age, overweight, and standard measures of arterial stiffness. Stress correction of carotid midwall strain strengthens its negative relations with age and indices of arterial stiffness, suggesting that assessment of carotid midwall mechanics may enhance noninvasive assessment of conduit artery compliance.

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