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Application of speckle tracking in the evaluation of carotid artery function in subjects with hypertension and diabetes

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Abstract

Background—Speckle tracking enables direct tracking of carotid arterial wall motion. Timing intervals determined with carotid speckle tracking and slopes calculated from carotid artery area (CAA) versus cardiac cycle curves may provide further information on arterial function and stiffness. The proposed arterial stiffness parameters were examined in healthy controls (n=20), non-diabetic hypertensives (n=20), and type-II-diabetics (n=21).

Methods—Bilateral ECG-gated ultrasonograms of the distal common carotid were acquired with a 12-MHz vascular probe. Four timing intervals were derived from speckle tracked carotid arterial strain (CAS) curves: 1) carotid pre-distension period (PDP), 2) peak CAS time (PCAST), 3) arterial distension period (ADP), and 4) arterial diastolic time. In addition, CAA curves were recorded over the cardiac cycle and sub-divided into 4 segments S1–S4, relating to arterial distention and contraction periods.

Results—Mean far-wall PDP and peak CAS time were more delayed in diabetics and hypertensives than in controls. Global mean ADP was prolonged and arterial diastolic time was shorter in hypertensives and diabetics versus controls. Slopes of segments S2 and S4 were markedly steeper in the hypertensives/diabetics combined group compared with healthy controls (p=0.03, and p=0.02, respectively).

Conclusion—Speckle tracking based measures of arterial stiffness may provide potential additive value in assessing vascular function in patients at risk for cardiovascular disease.

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Keywords

arterial-stiffness; speckle-tracking; carotid-artery

Introduction

Carotid arterial strain (CAS) measured using ultrasound based distensibility is a method for assessing local arterial stiffness.¹ Distensibility based CAS measures have been shown to be associated with risk factors for cardiovascular disease² and with incident stroke.³ More recently, along with other groups, we reported that ultrasound based CAS can be measured using speckle tracking,^{4, 56} that CAS measured using speckle tracking was lower in subjects with diabetes mellitus (DM) and that this may be a more sensitive measure than conventional local measures of CAS.⁷ In addition to measuring CAS, speckle tracked strain curves can be used to provide other information such as the timing of various events (example, time from ventricular systole to the onset of arterial expansion, time to peak arterial expansion, time spent in expansion and recoil and the rate of these changes) in the arterial wall over the course of the cardiac cycle. Non-invasive measures of cardiac time intervals have been shown to have value in assessing cardiac function.⁸ However, limited data exist with respect to the importance of timing intervals in the evaluation of arterial health.

We aimed to determine if **a)** carotid artery strain measured by speckle tracking, which we have shown to be lower in diabetics⁷ is also lower in subjects with hypertension when compared to healthy individuals, and, **b)** if duration of various events in the arterial cycle—namely expansion and recoil, and **c)** slopes of the carotid artery area over the cardiac cycle, as obtained with speckle tracking, can provide additional information on vascular function as assessed by CAS. Additionally, we evaluated if the above parameters were related to hypertension and DM, disease states known to be associated with increased arterial stiffness.

Methods

Study Population

Subjects for our current analysis were selected from an ongoing study whose aim is to describe carotid arterial strain in various states of health. From a total of 102 individuals who were recruited at the noninvasive cardiac laboratory of our local county hospital (Ben Taub General Hospital), we selected 21 individuals with DM, 20 hypertensives and 20 healthy controls such that they were matched for age and gender. The differences in CAS between individuals with DM and healthy controls has previously been published.⁷ Hypertension was defined as presence of the ICD-9 code of 401.0 in the subject's medical problem list or active use of antihypertensive medications. Subject recruitment and carotid ultrasound were performed at any time during the day with no consideration being given to intake of food, caffeine, alcohol, tobacco, or vasoactive medications as we believe that this scenario represents conditions encountered more typically in a clinical setting. Exclusion criteria included known carotid stenosis greater than 70%, history of carotid stenting or carotid endarterectomy, history of radiation therapy to the neck, clinically significant aortic valve disease, any persistent arrhythmia, or a known life expectancy less than 6 months.⁷ The study was approved by the local Institutional Review Board, and written informed consent was obtained from all participants.

Ultrasound Image Acquisition

Acquisition of carotid ultrasound images and segmental carotid strain analyses were conducted as previously described.⁷ All subjects were interviewed and scanned by the same

study investigator. Briefly, the distal common carotid artery (CA) was imaged 1-cm inferior to the carotid bulb [mean 77.6 frames per second (fps) (standard deviation (SD) 7.9)] in transverse section with electrocardiography (ECG)-gating over 3 cardiac cycles using a 14 MHz M12L vascular transducer (Vivid 7 echocardiography instrument, GE Healthcare, Waukegan, WI). Images were exported in Digital Imaging and Communications in Medicine (DICOM) format for offline analysis with each subject being assigned a unique code.

Carotid Arterial Strain (CAS) Analysis

Ultrasound scans were uploaded to a computer workstation equipped with a speckle tracking software package (2D Cardiac Performance Analysis, TomTec, Germany). TomTec provided the analysis software but otherwise had no input into the study design, data accrual, analysis, or manuscript preparation. Details of the CAS analysis by speckle-tracking have been previously published.⁷ Briefly, circumferential CAS measures were obtained in six segments as in the myocardial short-axis views in segments of the distal common carotid artery free of plaque. Arterial segments located anteriorly (n=3) were identified as near wall segments; those inferiorly, as far wall segments (n=3). Peak systolic circumferential strain values were measured and averaged (i.e., mean of the peak) for all six segments and then separately for the three far wall segments to yield a global net and far wall average CAS, respectively. We have reported that these two measures have the greatest inter-visit and inter-/ intra-reader reproducibilities.⁷ These values were averaged over the 3 cardiac cycles and over both left and right sides to obtain one net global and far wall CAS average per individual. Luminal CAS (i.e., traditional method) was measured using maximum and minimum carotid lumen diameters averaged over 1 cm of the longitudinal distal common carotid, 1 cm inferior to the carotid bulb.

Time Intervals

Four time intervals were measured. The first measure was the time from start of electrical systole (i.e., start of the QRS complex on electrocardiography) to the time at the peak carotid arterial strain value i.e., peak carotid arterial strain time [peak CAS time] (Segment A, on Figure 1). However, after the start of electrical cardiac systole, the carotid artery continued to contract to a minimum value (Figure 1) (due to the delay between electrical cardiac systole and carotid artery systole). This time interval, between onset of electrical systole and the CAS minimum, was called the pre-distension period (PDP, Segment B on Figure 1). The time difference between the measured peak CAS time and PDP constituted the arterial distension period (ADP, Segment C on Figure 1). Finally, the arterial diastolic time was calculated as the time from peak carotid arterial strain to the end of the cardiac cycle (Segment D on Figure 1).

The PDP includes the electrical-mechanical delay in the onset of myocardial systole, isovolumic contraction period, the mechanical systole of the heart, and, finally the propagation of the pulse through the arterial tree to the distal common carotid artery. While the isovolumic contraction time can vary depending on the afterload experienced by the heart, in general, it increases with increasing myocardial stiffness (i.e., takes more time). On the other hand, stiffer vessels mean faster propagation of the pulse wave (i.e. less time). The PDP therefore included information related to both myocardial and the arterial tree's performance but may be difficult to interpret due to the opposite effects on the isovolumic contraction time and pulse wave propagation. The ADP, on the other hand, represents the time taken for the vessel to go from its minimum to maximum dimension and would be a function of the local pressure driving arterial distension and the intrinsic stiffness of the artery. The peak CAS time is a combination of both PDP and ADP. Finally, the arterial diastolic time denotes the arterial contraction time from peak distension to the end of the

cardiac cycle and includes a period when the aortic valve is closed and hence a period where there is no cardiac influence of the vascular properties of the carotid artery.

Carotid Artery Area (CAA) Curves and Slopes

As previously noted, changes in the carotid artery area over the cardiac cycle or distensibility have been used as a measure of arterial stiffness.⁹ Changes obtained by speckle tracking in carotid arterial area over the cardiac cycle can therefore provide an additional method to evaluate distensibility. The software analysis package used to estimate carotid artery strain also provides the opportunity to export the carotid artery luminal area for discrete time points over the cardiac cycle. The curves also provide an opportunity to study rate of change (slopes) which should be related to the local distending pressure but in addition to the properties of the arterial wall. However, while the circumferential CAS analysis can be performed with a minimum of 3 carotid segments, the CAA curve requires all 6 segments described above. Imaging artifacts such as shadowing or anatomical variations such as short-neck length contributed to impaired image quality and as a result, a total of 9 patients (6 hypertensives and 3 diabetics) were not included for this portion of the analysis resulting in a subset consisting of 20 healthy controls, 15 subjects with hypertension, and 17 subjects with diabetes (52 out of 61 subjects).

The carotid artery area curve measurements were recorded with a frame-rate of 78.3 ± 9.2 frames per second which was similar to the temporal resolution for the CAS analyses ($p=0.55$). Due to potential variations across multiple cardiac cycles, the CAA curves were averaged over 3 cardiac cycles using an in-house developed automatic ensemble (collective) means algorithm. The ensemble-means methodology permits averaging over discrete data points recorded over multiple cardiac cycles of different lengths and varying temporal resolution.¹⁰ The present ensemble-means algorithm uses the QRS onset times from the 3 cardiac cycles to align and subsequently interpolate the CAA curves. This process results in an ensemble-means CAA curve which is illustrated in Figure 2 for a normal, hypertensive, and diabetic subject.

From these ensemble-means curves we calculated: **i)** CAA at end vascular diastole which identifies the beginning of arterial distention and was defined as the smallest area in the ensemble-means CAA curve (Figure 3); **ii)** carotid artery area at peak of vascular systole which was defined as the largest area in the CAA curve and marks peak distention of the CA. End of vascular diastole and peak of vascular systole were used to calculate: **iii)** slopes of four distinct segments of the CAA curve which are labeled S1–S4 and are illustrated in Figure 3; **iv)** carotid artery distensibility, computed as (carotid artery area at peak of vascular systole - carotid artery area at end of vascular diastole); and **v)** carotid artery distensibility normalized to the carotid artery area at EVD was calculated as (carotid artery area at peak of vascular systole - carotid artery area at end of vascular diastole)/(carotid artery area at end of vascular diastole).

Slopes of segments S1–S4 quantitatively assess the shape of the CAA curve and provide insight into the dynamics of arterial distension and arterial relaxation over the cardiac cycle. The slopes S1 and S2 (each corresponds to 50% of the distance between end of vascular diastole and peak of vascular systole on the time axis) describe arterial distention, which is due to the distending pressure¹¹ while slopes S3 and S4 (again divided such that they were equally distributed on the time axis segment peak of vascular systole to end of the cardiac cycle) describe the relaxation of the CA, where the diastolic blood pressure plays an important role. Figure 3 also shows a second peak/shoulder in the CAA curve. While we did not record simultaneous arterial pulse wave measurements in this study, the second peak/shoulder in the CA area curve could represent the dicrotic notch that is thought to be closely related to the aortic valve closure.¹² In a secondary analysis, we recalculated slopes S3 and

S4 for 2 curve segments: peak of vascular systole to second peak/shoulder ($S3_n$), and from second peak/shoulder to the end of the cardiac cycle in the CAA curve ($S4_n$). Since the results were similar whether we used $S3/S4$ or $S3_n/S4_n$ we present the results based on slopes $S3/S4$ only. All markers were automatically calculated with algorithms implemented in Matlab Version 7.8.0 (64-bit). All calculations were performed with 2.83-GHz 64-bit PC equipped with an Intel Quad Core Q9550 processor and 8 GB memory. The calculation of an ensemble-means CAA curve and the extraction of all salient markers required approximately 0.09 seconds per dataset.

Statistical Methods

Timing intervals were examined with and without adjustment for cardiac cycle length, since cardiac cycle length has been previously shown to have a strong correlation with left ventricular ejection time¹³, and more recently with arterial distension periods in healthy individuals.¹⁴ For illustrative purposes, all slopes were multiplied by a factor of 1,000. For all analyses, significance was set at a p -value < 0.05 . The Shapiro-Wilk test was used to assess the non-normality of continuous variables. Appropriate two-tailed parametric and non-parametric omnibus tests for comparisons among the 3 groups (e.g., analysis of variance [ANOVA] and Kruskal-Wallis tests, respectively) were employed to compare the participant characteristics, strain measures, time intervals, and slopes of the CAA curves. If the omnibus test proved significant, pairwise comparison were performed between the groups using appropriate parametric and non-parametric tests (e.g., two sample t -tests and Wilcoxon rank-sum tests, respectively). As appropriate, Bonferroni corrections were applied to provide the “corrected p -value”. Categorical tests (e.g., χ^2 and Fisher’s exact tests, respectively) were used to assess nominal variables. Differences of the carotid artery area curves between controls and the hypertensive/diabetic group were analyzed with the non-parametric Wilcoxon-Mann-Whitney test.

Non-normal parameters, as determined by the Shapiro-Wilk test, were normalized using log-, or square-root transformation based on ladder of powers analyses. The Pearson correlation coefficient (r) was calculated and the strength of correlations described as weak ($r < 0.4$), moderate ($0.4 \leq r < 0.7$), or strong ($r \geq 0.7$).¹⁵ Logistic regression models were used to assess the discriminative ability of the arterial stiffness markers to correctly identify diabetic and hypertensive subjects (2 medical conditions that have been associated with impaired arterial function) from healthy controls. The area under the receiver operating curve (AUC) was calculated using the (concordance statistics [c-statistic]) of logistic regression models and the incremental value of combining US-based markers of arterial stiffness were assessed with the AUC (c-statistic).¹⁶

Results

Overall, the population ($n=61$) was middle aged (mean $57.5 \pm$ [standard deviation (SD) 10.1] years) with 51% of the sample being women. Characteristics (other than hypertension/diabetes status) were similar among the 3 groups except for heart rate, medication use, carotid intima media thickness and plaque prevalence (Table 1). However, heart rate for hypertensives was similar to those with DM (corrected $p=0.18$). Individuals included in the sub-group analysis ($n=52$) for the CA area curves had similar baseline characteristics compared with the 61 subjects.

Carotid artery time intervals

No differences were noted between hypertensives and diabetics for any comparisons related to the time intervals. The absolute arterial pre-distension period (PDP) was prolonged in hypertensives vs. controls for the far wall averaged CAS (Table 2), but not the global net

averaged CAS. For subjects with diabetes the absolute arterial distension period (ADP) was shorter for both far wall and global net averaged CAS (Table 2). The arterial diastolic time was significantly shorter in hypertensives and diabetics vs. healthy controls using either far wall or global average CAS. When normalized for the cardiac cycle length, the PDP and peak CAS time were prolonged in hypertensives and diabetics vs. in controls for both far wall and global averaged CAS while a similar trend was seen for the ADP obtained from the global net averaged CAS curve, but not for that obtained from the far wall averaged CAS curve (Table 3). On the other hand, arterial diastolic time was significantly shorter for diabetics and hypertensives for global averaged CAS while a strong trend was seen for the far wall CAS.

When additionally adjusted for far wall CAS, the differences for the comparison between individuals with DM and healthy controls persisted for PDP ($p=0.02$), peak CAS time ($p=0.01$) and arterial diastolic time ($p=0.05$), but for hypertensives only PDP was different from controls (PDP: $p=0.02$; peak CAS time: $p=0.06$; arterial diastolic time: $p=0.45$). When further adjusted for systolic blood pressure, the differences between hypertensives and controls persisted for PDP ($p=0.009$) and became significant for peak CAS time ($p=0.02$). For the comparison between diabetics and controls only a trend was observed for differences in PDP ($p=0.06$) and peak CAS time ($p=0.09$), respectively. Arterial diastolic time and ADP were no longer significant after further adjustment for systolic blood pressure.

Slopes of the Ensemble-Means Carotid Artery Area Curves

Again, no differences were noted for the slopes when hypertensives and diabetics were compared with each other. When compared individually with healthy controls, a trend toward steeper slope S2 was observed in diabetics ($p=0.07$) but not for hypertensives (Table 4). After adjusting for strain slope S2 became significantly steeper in diabetics versus normals ($p=0.03$) and after remained significant after further adjusting for systolic blood pressure ($p=0.03$). Similar to slope S2, slope S4 was also significantly steeper in diabetics ($p=0.02$) but not for hypertensives when compared with healthy controls. However, when adjusted for strain, slope S4 was significantly steeper in both diabetics ($p=0.0002$) and hypertensives ($p=0.03$) when they were each compared to healthy controls. The significance remained even with further adjustment for systolic blood pressure (Table 4). For slopes S1 and S3, no differences were noted for the various comparisons.

When we combined hypertensives and diabetics together as a group and compared them with the healthy controls a similar result was seen with slopes of the S2 segment (0.186 ± 0.1 vs. 0.116 ± 0.08 , $p=0.03$) and S4 segment (-0.054 ± 0.03 vs. -0.040 ± 0.01 , $p=0.02$) but not that of S1 and S3 being significantly different from healthy controls. When further adjusted for carotid arterial strain and systolic blood pressure, slopes S2 and S4 of the CAA curve remained significantly steeper for hypertensives/diabetics combined compared with healthy controls [with adjustment for strain; $p=0.02$ for S2 and $p=0.0003$ for S4 and with additional adjustment for systolic blood pressure $p=0.01$ for S2 and $p=0.0004$ for S4].

Carotid Arterial Strain

For the total population ($n=61$), the far wall average CAS and global net CAS were $4.46\pm1.51\%$ and $4.51\pm 1.28\%$, respectively. The far wall average and global net CAS measures were lower in hypertensives compared with controls (corrected $p=0.007$) but not significantly different from those in diabetics.

Carotid Artery Area Curves Measurements

Compared with healthy controls, hypertensive and diabetic individuals had dilated minimum and maximum carotid artery cross-sectional areas measured at end of vascular diastole

($0.55 \pm 0.09 \text{ cm}^2$ vs. $0.40 \pm 0.07 \text{ cm}^2$, $p < 0.001$), and peak of vascular systole, respectively ($0.60 \pm 0.14 \text{ cm}^2$ vs. $0.45 \pm 0.08 \text{ cm}^2$, $p < 0.001$). Carotid artery areas at end of vascular diastole and peak of vascular systole remained significantly different when adjusted for strain and systolic blood pressure for healthy controls compared with hypertensive ($p = 0.01$ for both adjustments) and for controls compared with diabetics ($p = 0.03$ for both adjustments). There was no significant difference in absolute distensibility of the CA area between controls and diabetics/hypertensives. However, CA area distensibility normalized to end of vascular diastole area was significantly larger in healthy controls compared with hypertensives and diabetics (0.12 ± 0.04 vs. 0.095 ± 0.03 , $p = 0.03$). When adjusting for systolic blood pressure, normalized CA area distensibility remained significantly different between hypertensives/diabetics combined and controls ($p = 0.01$).

Correlations

Pearson correlation coefficient analyses was performed between CAS measures, time intervals, CAA curves measures and slopes. CAS measures showed a strong correlation with normalized CA distensibility but not with time intervals, and slopes of the CAA curve (Supplemental table S1). When slopes were correlated with time intervals only the slope of segment S2 (CA distention segment) showed a moderate inverse correlation with peak CAS time ($r = -0.41$, $p = 0.003$).

Benefits of Combining Carotid Arterial Strain, Timing Intervals, and Slopes of Carotid Artery Area Curve

Logistic regression models were used to assess CAS measures, time intervals and CAA curve slopes to discriminate hypertensive and diabetic subjects from healthy controls.

All parameters added to CAS increased to a varying degree the c-statistics for discriminating diabetics and hypertensives from controls. Adding slope S2 of the CAA curve to CAS improved the c-statistic non-significantly ($p = 0.25$) from 0.828 (95% CI = 0.717–0.939) to 0.877 (CI = 0.783–0.970) while adding slope S4 significantly improved the c-statistic to 0.958 (CI = 0.899–1.000; $p = 0.008$). The addition of normalized CA distensibility to CAS non-significantly increased the c-statistics to 0.845 (CI = 0.737–0.954; $p = 0.62$). Adding both slopes S2 and S4 together to CAS, significantly increased the AUC to 0.961 (CI = 0.903–1.000; $p = 0.007$). Adding the four timing intervals (PDP, peak CAS time, ADP, and arterial diastolic time) to CAS, non-significantly increased the c-statistics to 0.898 (CI = 0.816–0.981; $p = 0.11$). Finally, adding slopes S2 and S4 and the four timing intervals to CAS resulted in the largest change in the AUC which significantly increased to 0.986 (CI = 0.965–1.000; $p = 0.005$).

Discussion

The three principal findings of this study were that compared to healthy controls: 1) timing intervals (normalized to the cardiac cycle length) differed in groups with diabetes and hypertension; 2) the slopes of the carotid artery area curve were steeper and cross sectional areas of the CA were larger in groups with diabetes and hypertension; and 3) carotid arterial strain was lower in hypertensives, a finding similar to our prior results in diabetics.⁷ In addition, correlation analyses and logistic regression models suggested that time intervals and especially slopes of the CAA curves are additive to CAS in predicting diabetes and hypertension status. Therefore, adding the time intervals and slopes to the speckle tracked CAS can further enhance our knowledge on arterial function through the cardiac cycle.

Arterial stiffness has been associated with an increased risk of stroke and cardiovascular disease in large epidemiological studies such as the Atherosclerosis Risk in Communities

(ARIC), the Rotterdam Study, and the Multiethnic Study of Atherosclerosis (MESA).^{17–19} Various methods to measure arterial stiffness have emerged over the years including local (example ultrasound based measurement of distensibility) and systemic (example pulse wave velocity) measures. Of these measures, pulse wave velocity has shown the strongest associations with cardiovascular disease.¹⁷ Advances in ultrasound technology could allow improved local assessment of arterial stiffness and hence, perhaps, in the future allow the demonstration of stronger associations between local arterial stiffness and cardiovascular disease similar to pulse wave velocity. Speckle tracking is one such advance which allows calculating changes in the carotid artery wall over the cardiac cycle with high spatial and temporal accuracy. Our study adds to the growing body of literature related to measurement of CAS as assessed by speckle tracking^{4–67}, and further expands on the potential value of speckle tracking by evaluating and reporting on time intervals and slopes of the carotid artery area curves which seem to have incremental value beyond CAS. Reesink et al. described the feasibility of extracting cardiac systolic time intervals from carotid artery distension waveforms.²⁰ To our knowledge, we are among the first to describe differences in carotid time intervals from strain curves acquired with speckle-tracking in patients with cardiovascular risk factors.

Koivistoinen et al. examined arterial distension periods indirectly with “arterial tension times” (defined as the time difference between the onset of arterial distension induced by stroke volume and maximal integrated arterial distension) derived from whole-body impedance cardiography and found the absolute tension time to be inversely related to the number of cardiovascular risk factors and with heart rate but did not further investigate the relationship with heart rate.²¹ We observed a similar trend in our absolute arterial distension periods among the 3 groups (Table 2) but when the time intervals were indexed for cardiac cycle lengths, the relationship between carotid time intervals (except for arterial diastolic time) and cardiovascular risk factors was reversed. In other words, patients with cardiovascular risk factors had a relatively longer arterial distension period compared with healthy controls despite distensibility/CAS being greater in the healthy controls. In addition, the pre-distension period was longer in those with diabetes and hypertension. Taken together, these findings suggest that cardiac contraction and pressure generation may be relatively delayed as is the time required to distend the artery to its maximum dimension in the setting of increased vascular stiffness. This in turn provides the artery in a normal individual a greater amount of time to recoil to its minimum dimension, as can be seen based on the arterial diastolic time interval.

Our finding that some of the slopes were steeper and added to CAS in hypertensives/diabetics when compared to healthy controls was of interest as well as this suggests that the rate of change of arterial area in the hypertensives and diabetics is different when compared to healthy individuals. Hence slopes may also be of interest in the assessment of vascular function. Although slopes are commonly calculated for pulse wave velocity and transit time curves,²² this is the first application that we know of to carotid artery area versus cardiac cycle (time) curves.

Finally our analysis showing that circumferential carotid strain is lower in hypertensives adds to previous reports (including ours) on the potential value of circumferential carotid artery strain measured by speckle tracking in the evaluation of arterial stiffness. Bjallmark et al., Oishi et al., Park et al., and Catalano et al. demonstrated that common carotid artery strain measures were significantly and inversely correlated with increasing age and the number of cardiovascular risk factors^{23–26} while we have previously shown that CAS was lower in diabetics.⁷ In the current analysis we extend our findings and demonstrate that hypertensives had lower CAS as well.

Hypertension has long been established as a strongly independent, yet modifiable, determinant of arterial diameter enlargement, wall hypertrophy, and increased wall stiffness.^{27, 28} Its effects on stiffening have been postulated to be mediated through passive recruitment of stiffer collagen fibers on top of the elastin lamellae²⁹ and through active arterial remodeling via the renin-angiotensin-aldosterone system.³⁰ In addition to its association with renin-angiotensin-aldosterone system, diabetes has also been shown to be associated with arterial stiffening, but through crosslinking of the vasculature by advanced glycation endproducts.³¹ In our analysis, although the majority of the diabetics were hypertensives as well, no major differences between these individuals and those with hypertension alone were noted. This may reflect the relatively smaller sample size in our analysis; however, the relative importance/ contribution of both diabetes and hypertension towards arterial stiffening should be further evaluated.

Previous observations have reported that carotid arterial stiffness may be more strongly linked with hypertension than with diabetes.³²

Clinical Implications of Ultrasound-Based Measures of Arterial Stiffness

From a clinical perspective the measurement of carotid arterial strain, time intervals, and slopes of carotid artery area curves can be easily obtained with standard ECG-gated vascular ultrasonography imaging of the carotid arteries without the need of additional equipment, other than software to quantify strain and slopes of CAA curves. The calculation of the arterial stiffness measures presented in this study mainly requires post-processing for which tools can easily be developed. Currently, we used a commercially available software (2D Cardiac Performance Analysis, TomTec, Germany) developed to measure cardiac strain and applied it to measure carotid strain, the timing intervals and to generate the area curves while we developed an algorithm to measure the slopes. In the future, carotid/ vascular specific software will need to be developed and algorithms such as our ensemble means algorithm to measure slopes can be easily incorporated. Whether the timing intervals, slopes and CAS could be additive to measures of atherosclerosis such as carotid intima media thickness and plaque estimation will need to be further evaluated. Additionally, if the time intervals (especially the pre-distension period) can be further characterized, additional information on the ventricular-arterial interaction or coupling which is thought to be very important in cardiovascular diseases such as heart failure with preserved left ventricular function can be better evaluated. Finally, these time intervals and slopes may have value in clinical research to study the effect of various medications used in the treatment of hypertension and diabetes and should be evaluated as a potential surrogate marker.

Limitations

We used brachial blood pressures instead of local carotid pressures. These have been shown to be different from each other and to undergo different remodeling effects even within an individual.²⁸ However, in states of disease the brachial and carotid pressures tend to be more similar than in healthy normal individuals and therefore if anything we would have biased the results towards null. We adapted ultrasound systems and analysis tools intended for myocardial analysis for vascular applications and used DICOM images instead of raw ultrasound data. Ideally, systems and platforms dedicated for vascular use may improve the reliability of arterial strain measurements and should be developed. We evaluated one segment of the distal common carotid, and this may not be representative of the entire vascular tree. The sample sizes were small, and we did not examine the association of carotid strain with the severity or duration of hypertension or diabetes. Subjects with hypertension or diabetes had significantly higher heart rates than controls. However, we presented models with and without indexing for the cardiac cycle length. Finally the pre-

distension period may have varied depending on the path length (i.e., heart to distal common carotid). However, this should not have affected the arterial distension period or slopes.

Future Directions

Optimization of speckle-tracking systems for vascular applications should be pursued. Carotid strain measures of different carotid artery segments still need to be investigated. With further validation and improvement in techniques, carotid arterial strain measures in combination with echocardiography should be used to further assess their value in understanding the ventricular-arterial coupling relationship.

Conclusion

Magnitude and timing of arterial strain and slopes of carotid artery area curves have potential additive value in assessing vascular function in patients at risk for cardiovascular disease and should be further investigated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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List of abbreviations

CAA	carotid artery area
PDP	carotid pre-distension period
ADP	arterial distension period
CAS	carotid arterial strain
CA	carotid artery
DM	diabetes mellitus

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Figure 1. Carotid arterial strain curves with timing intervals

Carotid arterial strain curves with (A) peak carotid arterial strain time, (B) arterial pre-distension period, (C) arterial distension periods relative to the onset of the QRS on electrocardiography, and (D) arterial diastolic time.

Figure 2. Ensemble means carotid artery area curves

Carotid artery area (CAA) curves over 3 cardiac cycles from a normal subject and subjects with hypertension and diabetes (all 3 subjects were women). **Left panel:** CAA raw curves; **Right panel:** corresponding ensemble-means CAA curves.

Figure 3. Carotid artery area curves with an illustration of the corresponding slopes
 Ensemble-means carotid artery area (CAA) curve from a healthy normal with salient markers. PVS=peak vascular systole, EVD=end vascular diastole; ECC=end of the cardiac cycle, PVS-ECC indicates the fraction of the cardiac cycle from PVS to the end of the cardiac cycle. DN marks the dicrotic notch. Slopes S1–S4 were obtained for the respective segments of the CAA curve over the cardiac cycle.

Table 1

Baseline characteristics of the controls, hypertensives, and diabetic individuals.

Characteristic	Controls (n = 20)	Hypertensives (n = 20)	Diabetics (n = 21)	P-values
Age (years)	56.6 (8.4)	58.8 (13.1)	57.1 (8.4)	0.77
Male (%)	50	45	52.4	0.89
Caucasian (%)	30	25	23.8	0.89
African-American (%)	30	40	38.1	0.78
Hispanic (%)	25	25	33.3	0.79
Asian (%)	15	10	4.76	0.55
Systolic BP (mm Hg)	120.8 (11.9)	128.8 (19.4)	127.7 (22.5)	0.34
Diastolic BP (mm Hg)	73.8 (7.3)	77.9 (13.5)	76.8 (12.0)	0.49
Pulse Pressure (mm Hg)	47.0 (6.9)	50.9 (11.1)	50.9 (14.2)	0.45
Heart Rate (bpm)	63.3 (10.1)	72.3 (12.6)	79.0 (9.7) [‡]	0.0001
Hypertensive (%)	0	100 [‡]	76.2 [‡]	<0.0001
Current Smoker (%)	0	2.6	23.8	0.08
Past Smoker (%)	30	20	38.1	0.45
C-IMT (mm) [€]	0.736 (0.122)	0.794 (0.135)	0.870 (0.147) [‡]	0.02
Plaque prevalence (%) [£]	5	40	52.4	0.003
Amiodarone	0	5	4.8	<0.0001
Beta Blocker (%)	0	80	76	<0.0001
Calcium Channel Blocker (%)	0	10	9.5	<0.0001

* All values are proportions or means (standard deviations).

[‡] corrected p <0.05 v. controls

[‡] corrected p <0.01 v. controls

[€] Carotid intima media thickness (C-IMT) for both carotids could be measured in 20 controls, 16 hypertensives and 17 diabetics

[£] Presence of plaque could not be evaluated in 1 artery (right carotid) for a hypertensive patient

Table 2

Absolute carotid artery time intervals by carotid arterial characteristic examined.

Variables (msec)	Controls	Hypertensives	Diabetics	P-values
Far Wall Average				
Pre-distension period	55.2 (22.8)	78.3 (29.7) ^I	72.6 (27.8)	0.006
Peak strain time	328.5 (63.9)	329.5 (66.2)	308.6 (43.3)	0.62
Arterial distension period	273.3 (48.8)	251.2 (54.1)	236 (36.4) ^I	0.045
Arterial diastolic time	648.5 (136.4)	517.4 (106.8) ^I	462.1 (96.3) ^I	0.0001
Global Net Average				
Pre-distension period	67.3 (31.3)	76.5 (31.4)	72.3 (20.4)	0.25
Peak strain time	341.8 (68.6)	337.4 (68)	312.2 (39.4)	0.24
Arterial distension period	274.5 (46.7)	260.9 (51.2)	239.9 (33.5) ^I	0.049
Arterial diastolic time	635.2 (113.5)	513.1 (109.4) ^I	457.4 (89.8) ^I	0.0001

* All values are means (standard deviations).

^I corrected p <0.05 v. controls

Table 3

Cardiac cycle fractions of carotid artery time intervals by carotid arterial characteristic examined.

Variables (%)	Controls	HTN	Diabetics	P-values		
[Cardiac cycle fractions]	Far Wall Average			Model 1	Model 2	Model 3
Pre-distension period	5.7 (2.2)	9.6 (3.7) ^{1,2,3}	9.6 (3.8) ^{1,2}	0.0001	0.01	0.01
Peak strain time	33.9 (5.3)	39.0 (4.9) ^{1,3}	40.5 (6.3) ^{1,2}	0.0009	0.02	0.02
Arterial distension period	28.2 (3.7)	29.4 (2.8)	30.9 (5.1)	0.09	0.19	0.19
Arterial diastolic time	64.6 (4.9)	60.6 (5.2) ¹	58.5 (7.0) ¹	0.006	0.06	0.06
Global Net Average						
Pre-distension period	6.8 (2.3)	9.3 (3.7) ¹	9.5 (2.8) ¹	0.0005	0.12	0.13
Peak strain time	35.1 (3.9)	39.9 (5.4) ^{1,2}	41.0 (5.6) ^{1,2,3}	0.009	0.02	0.03
Arterial distension period	28.3 (3.0)	30.7 (2.9) ¹	31.5 (4.6) ¹	0.02	0.10	0.11
Arterial diastolic time	64.4 (4.7)	60.2 (6.0) ³	58.6 (6.3) ^{1,2}	0.005	0.04	0.048

* All values are means (standard deviations). HTN= hypertensives.

P-values: Model 1= unadjusted; Model 2= adjusted for strain.

Model 3= Model 2 + systolic blood pressure.

¹ corrected p <0.05 v. controls for Model 1

² corrected p <0.05 v. controls for Model 2

³ corrected p <0.05 v. controls for Model 3

Table 4

Salient markers from ensemble-means CAA curves in normals, hypertensives and diabetics.

Variables	Controls (N=20)	HTN (N=15)	Diabetics (N=17)	P-values		
Slopes of the Ensemble Means Carotid Artery Area Curves				Model 1	Model 2	Model 3
Mean slope S1	0.232 (0.09)	0.200 (0.08)	0.245 (0.1)	0.41	0.27	0.24
Mean slope S2	0.116 (0.08)	0.170 (0.1)	0.201 (0.1) ^{2,3}	0.07	0.03	0.03
Mean slope S3	-0.087 (0.05)	-0.099 (0.06)	-0.106 (0.04)	0.27	0.11	0.13
Mean slope S4	-0.040 (0.01)	-0.050 (0.03) ^{2,3}	-0.058 (0.02) ¹⁻³	0.03	0.0003	0.0004
Areas of Ensemble-Means Carotid Artery Area Curves [cm ²]				Model 1	Model 2	Model 3
CA area at EVD	0.403 (0.07)	0.551 (0.14) ¹⁻³	0.545(0.04) ¹⁻³	<.001	0.007	0.008
CA area at PVS	0.452 (0.08)	0.602 (0.15) ¹⁻³	0.60 (0.12) ¹⁻³	<.001	0.007	0.009

* All values are means (standard deviations). HTN= hypertensives.

P-values: Model 1= unadjusted; Model 2= adjusted for strain.

Model 3= adjusted for strain, and systolic blood pressure.

¹ corrected p <0.05 v. controls for Model 1

² corrected p <0.05 v. controls for Model 2

³ corrected p <0.05 v. controls for Model 3