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***In vivo* carotid strain imaging using principal strains in longitudinal view**

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Abstract

Carotid plaque rupture can result in stroke or transient ischemic attack that can be devastating for patients. Ultrasound strain imaging provides a noninvasive method to identify unstable plaque likely to rupture. Axial, lateral and shear strains in carotid plaque have been shown to be linked to carotid plaque instability. Recently, there has been interest in using principal strains, which do not depend on angle of insonification of the carotid artery for quantifying instability in plaque along the longitudinal view. In this work relationships between angle dependent axial, lateral and shear strain along with axis independent principal strains are compared. Three strain indices were defined, 1) Average Mean Strain (AMS), 2) Maximum Mean Strain (MMS) and 3) Mean Standard Deviation (MSD) to identify relationships between these five strain image types in a group of 76 *in vivo* patients. The maximum principal strain demonstrated the highest strain values when compared to axial strain for all patients with a linear regression slope of 1.6 and a y intercept of 2.4 percent strain for AMS. The maximum shear strain when compared to shear strain had a slope of 1.15 and a y intercept of 0.21 percent for AMS. Next, the effect of insonification angle, which is the angle subtended by the artery at the location of plaque was studied. Patients were divided into three sub groups, i.e. less than 5 degrees ($n = 31$), between 5 and 10 degrees ($n = 24$) and above 10 degrees ($n = 21$). The angle of insonification did not make a significant difference between the three angle groups when comparing the relationship between the angle dependent and independent strain values.

Keywords

elastography; carotid strain imaging; strain indices; principal strains; ultrasound

Introduction

Carotid artery plaque rupture can result in stroke, which is the leading cause of long-term disability and the 5th leading cause of mortality in the United States (Benjamin *et al.*, 2018). Therefore, it is clinically important to identify plaque prone to rupture. Fibrous plaques, which appear more echogenic with ultrasound imaging, are considered less prone to rupture when compared to plaques that have a larger lipid component, intraplaque hemorrhage, appear more echolucent on ultrasound and/or have a thin fibrous cap (Langsfeld *et al.*, 1989; Salem *et al.*, 2014). Ultrasound strain imaging (Ophir *et al.*, 1991; Varghese, 2009) can provide useful information regarding plaque tissue composition based on the strain distribution. Higher strain values are associated with softer tissues that can deform more (i.e. plaque with more lipid and/or hemorrhage content). Lower strain values are associated with stiffer tissue (i.e. plaque with more fibrous tissue).

Carotid ultrasound strain imaging utilizes the natural cardiac pulsation of the carotid artery for estimating carotid plaque strain *in vivo* and non-invasively (Shi *et al.*, 2008; McCormick *et al.*, 2012; Ribbers *et al.*, 2007; Hansen *et al.*, 2016). Axial strain in the direction of the ultrasound beam propagation direction, lateral strain perpendicular to the beam and shear strain can be estimated. However, underestimation of directional strain values may occur when the artery is not exactly aligned perpendicular to the beam propagation direction, necessitating the use of principal strain values (Nayak *et al.*, 2018). Moreover, due to the heterogeneous nature of plaque, and varying degree of stenosis that may be present, there are instances in which although the artery may be perfectly aligned to the ultrasound beam, the surface of the plaque will not be perfectly aligned to the ultrasound beam and therefore the direction of principal strain may vary in different segments of the plaque. (Mercure *et al.*, 2014).

Several strain imaging studies have utilized principal strain for various reasons as listed below (Mercure *et al.*, 2014; Nayak *et al.*, 2018; Lee *et al.*, 2008; Fung-Kee-Fung *et al.*, 2005; Zervantonakis *et al.*, 2007; Chen and Varghese, 2009). Myocardial elastography applications use principal strain to overcome the angle dependence of lateral and axial strain and centroid dependence of polar strains (Lee *et al.*, 2008; Fung-Kee-Fung *et al.*, 2005; Zervantonakis *et al.*, 2007). Angle independent strains have also been reported for carotid strain imaging (Nayak *et al.*, 2018; Mercure *et al.*, 2014; Fekkes *et al.*, 2018; Li *et al.*, 2019; Porée *et al.*, 2015). (Mercure *et al.*, 2014) used a local angle compensation technique to account for heterogeneity in plaque and transducer angle dependence of axial strain. A similar problem of finding the centroid is posed in transverse carotid imaging when calculating radial and circumferential strains. (Nayak *et al.*, 2017) used principal strains for transverse carotid strain imaging to estimate strain independent of the center of the lumen. (Nayak *et al.*, 2018) demonstrated that for longitudinal strain imaging in healthy volunteers, principal and axial strains were similar for straight arteries while for arched or angled arteries the principal strains presented with higher values when compared to their axial strain counterparts.

Typically, estimation of lateral displacement and strain is challenging due to the reduced spatial resolution in the lateral direction. One important assumption made for principal strain

estimation is that reliable lateral displacement or strain estimates can be computed. Several studies have tackled this problem using different techniques. Compounded plane wave imaging was shown to improve the lateral resolution for carotid strain imaging (Nayak *et al.*, 2017; Korukonda *et al.*, 2013). Another approach is to use lateral interpolation of the radio frequency (RF) data coupled with interpolation within the similarity matrices used for displacement tracking in elastography applications (Céspedes *et al.*, 1995; McCormick and Varghese, 2013). RF interpolation is computationally expensive and does not provide significant advantages over interpolation in the similarity matrix (Lopata *et al.*, 2009). (Lopata *et al.*, 2009) reviewed the use of parabolic, cosine and spline interpolation and concluded that all interpolation techniques provided subsample estimates with similar accuracy. (Céspedes *et al.*, 1995) proposed the use of a sinc based reconstructive method, which provided unbiased estimates unlike curve fitting methods. (McCormick and Varghese, 2013) demonstrated that reconstructive 2D windowed sinc function provided unbiased estimates, which were better than using cosine or parabolic interpolation. They used a Nelder-Mead optimization technique to find the unbiased peak of the similarity matrix. Recently, (Meshram and Varghese, 2018) implemented this interpolation on a GPU by using an iterative parallel reduction scheme which allowed for lower computational time.

(McCormick *et al.*, 2012) implemented a Lagrangian carotid strain imaging algorithm which uses multi-level coarse to fine estimation along with signal stretching based on strain estimated from coarser levels to improve strain estimation in the finer levels thereby minimizing signal decorrelation (Chaturvedi *et al.*, 1998; Varghese and Ophir, 1997). Bayesian regularization of the normalized cross correlation based similarity matrices (McCormick *et al.*, 2011) and 2D windowed sinc interpolation for unbiased sub sample estimation was also implemented (McCormick and Varghese, 2013). A fast GPU implementation of these technique was presented in (Meshram and Varghese, 2018).

(McCormick *et al.*, 2012) also accumulated incremental displacements and estimated Lagrangian axial, lateral and shear strain values (axis dependent strains). Preliminary results on principal strain derived values (axis independent strains) was also presented (McCormick *et al.*, 2012). Axis dependent strains have been utilized in *in vivo* patient studies and all three strain distributions (axial, lateral and shear) have shown successful estimation of quantitative 'strain indices' that correspond to carotid plaque instability (Meshram *et al.*, 2017; Dempsey *et al.*, 2017; Wang *et al.*, 2016; Wang *et al.*, 2014; Naim *et al.*, 2013; Huang *et al.*, 2016; Huang *et al.*, 2017; Roy Cardinal *et al.*, 2017). (Wang *et al.*, 2016) also demonstrated a relationship between elevated values of strain indices to lower cognition scores for both symptomatic and asymptomatic patients with severely stenotic plaque. However, the symptomatic group presented with a stronger relationship than the asymptomatic group. (Meshram *et al.*, 2017) derived additional strain indices from plaque strain maps to characterize plaque vulnerability. These multi-feature classifiers provided better relationship to cognitive deficits than previous work. Recently, (Meshram *et al.*, 2019) demonstrated that while executive function had a similar negative relationship with strain for both groups, visuo-spatial, memory and language function only had a negative relationship with strain for symptomatic but not for the asymptomatic group. In addition, normalization to the systemic blood pressure, does not have a significant impact on classifiers based on these 'strain indices' (Varghese *et al.*, 2017).

Currently there are no *in vivo* studies on atherosclerotic patients with > 60% stenosis that have reported on principal strains in the longitudinal view. The aim of this work is to examine relationships between axis dependent and principal strain values for *in vivo* carotid plaque characterization in the longitudinal view for a group of 76 patients with advanced atherosclerosis.

We also evaluate for changes between axis dependent and principal strain values with insonification angle of the artery at the location of plaque. (Nayak *et al.*, 2018) reported for carotid walls of healthy subjects that the axial strain decreased with an increase in angle while the first principal strain remained relatively unaffected. It is of interest to examine if advanced *in vivo* carotid plaques present with a similar relationship. Two derived principal strain values are examined for this purpose. First, maximum absolute principal strain, which is the principal component with the highest magnitude, derived using Eigen value decomposition of the strain tensor. Second, maximum shear strain that can be estimated through rotation of the co-ordinate system.

Methods and Materials

Human subjects

Seventy-six patients scheduled for carotid endarterectomy at the University of Wisconsin-Madison Hospitals and Clinics underwent ultrasound and strain imaging prior to their surgery. This study was approved by the IRB at University of Wisconsin-Madison and informed consent was obtained from all patients. All patients met the clinical criteria for carotid endarterectomy according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET, 1999) and Asymptomatic Carotid Atherosclerosis study (ACAS, 1995). Forty-two (42) patients (55.26%) were symptomatic that is, they were previously diagnosed with a stroke or a transient ischemic attack. Thirty (30) patients (39.47%) were female. The average age along with standard deviation of the patient group studied was 69.97 (9.30) years. The average BMI and average percent stenosis along with their standard deviation were 28.95 (5.54) and 74.57 (13.65) respectively

Strain estimation

Radio frequency (RF) data loops were acquired on all the patients as part of the ultrasound and strain exam over several cardiac cycles. An Acuson Siemens S2000 system (Siemens Ultrasound, Mountain View, CA, USA) was used for acquiring the RF data with an 18L6 transducer with a center frequency of 11.4 MHz. A total of six views were acquired: common carotid, bifurcation and internal carotid on both left and right carotid arteries. Lagrangian Carotid Strain Imaging (LCSI) was performed offline on the datasets (McCormick *et al.*, 2012). The displacement tracking algorithm uses multi-level block matching (Shi and Varghese, 2007) with three levels to accurately estimate discontinuous displacements. The lower coarse levels are used to guide the higher finer levels (smaller processing kernel dimensions) which allows for displacement maps with high spatial resolution while also reducing false positives. Normalized Cross Correlation is used as a metric for block matching. Strain from the lower levels is also used to scale data blocks at higher levels to reduce signal decorrelation (Varghese and Ophir, 1997; Chaturvedi *et al.*,

1998). A Bayesian regularization algorithm is used to utilize information from neighboring data blocks and further improve the tracking accuracy (McCormick *et al.*, 2011). Details of the exact parameters used in the tracking can be found in (Meshram and Varghese, 2018). The displacement estimates are then accumulated on a mesh that is formed using manual plaque segmentations provided by an experienced sonographer and a Lagrangian description of strain is calculated on this mesh over an entire cardiac cycle. The sonographer manually segmented at least two and up to three end diastolic frames. The start and end of the cardiac cycle was determined by the sonographer's segmentations of the end-diastolic frames. A limitation of ultrasound strain imaging is that out of plane motion which occurs in the artery may cause signal decorrelation and affect the quality of results.

Principal Strain calculation

LCSI presents with a strain tensor for every estimated pixel within the segmented region. The axis dependent tensor has axial, lateral and shear components, which can be represented

as $E = \begin{bmatrix} \epsilon_{xx} & \epsilon_{xy} \\ \epsilon_{yx} & \epsilon_{yy} \end{bmatrix}$ Where $\epsilon_{xx} = \frac{\partial d_x}{\partial x}$ and $\epsilon_{yy} = \frac{\partial d_y}{\partial y}$ are the lateral and axial strain respectively

and $\epsilon_{xy} = \frac{\partial d_x}{\partial y}$ and $\epsilon_{yx} = \frac{\partial d_y}{\partial x}$ are lateral and axial shear strains respectively. Static equilibrium is assumed and only one shear strain is estimated defined as

$\epsilon_{xy}^* = \frac{1}{2} \left(\frac{\partial d_x}{\partial y} + \frac{\partial d_y}{\partial x} \right)$ (McCormick *et al.*, 2012). Hence we have the symmetric strain tensor

given by $E = \begin{bmatrix} \epsilon_{xx} & \epsilon_{xy}^* \\ \epsilon_{xy}^* & \epsilon_{yy} \end{bmatrix}$ To calculate the principal strain, we perform an Eigen value

decomposition, the solution to which is given by

$$\lambda_{1,2} = \frac{1}{2} \left(\epsilon_{xx} + \epsilon_{yy} \pm \sqrt{(\epsilon_{xx} - \epsilon_{yy})^2 + 4\epsilon_{xy}^{*2}} \right) \quad (1)$$

The principal strain component with the higher magnitude of the two λ' s is the maximum absolute principal strain and is defined as $\max \{ |\lambda_1|, |\lambda_2| \}$ (McCormick *et al.*, 2012). The square root term in equation (1) is the maximum shear strain and this can be calculated as $\frac{\lambda_1 - \lambda_2}{2}$.

Comparison of axis dependent strain values to principal strain derived values

For each of the seventy-six patients a single plaque RF data loop with low translational and out-of-plane motion whenever possible was selected. Data over a single cardiac cycle for the selected plaque was analyzed further for the comparison of the five different strain values axial, lateral, shear, maximum absolute principal strain and maximum shear strain. Three different indices from the entire plaque were quantified for the comparison. First, the Average Mean Strain (AMS) is computed as the mean of absolute strain values over entire plaque, averaged for an entire cardiac cycle. Second, Maximum Mean Strain (MMS) is the maximum value estimated over the entire cardiac cycle of the mean of the absolute strain value over the entire plaque. Third, Mean Standard Deviation (MSD) is the mean of the

standard deviation over entire plaque, averaged for an entire cardiac cycle. MSD is a strain index that was shown to have clinical diagnosis value in previous work (Meshram *et al.*, 2017). The AMS, MMS and MSD composite values were chosen as strain indices for comparison across the five different strain images as these are quantified across the entire plaque region. Hence any relationship between the ultrasound insonification angle and plaque orientation can be easily identified if present which may not be the case with the more localized strain indices over small and multiple regions of interest (ROI) with high strain across plaque utilized previously (Meshram *et al.*, 2017).

An automated algorithm is used to identify about 25 carotid wall points selected from evenly spaced intervals on both the near and far carotid walls with plaque to calculate the angle subtended by the plaque, defined as the insonification angle. A linear regression line is then fit across these points and the angle of this best fit line is computed as an estimate of the insonification angle. An example of this analysis is presented in figure 1. Figure 1 also demonstrates that multiple segmentations of plaque may be present in a given view. The figure on the right (b) depicts only the plaque regions in the near and far wall segmented in (a) where blue and violet colors are used to differentiate the two plaque regions. Red and green denotes the points on the wall while yellow and cyan colors represent the best-fit lines through these selected wall points of the respective plaque regions. In previous work (Meshram *et al.*, 2017) different views and additional segments within a view were allowed to be selected for axial, lateral and shear strains independently, depending on which view/segmentation provides higher magnitude strain indices. However, in this work since we are making a quantitative comparison across strain values only a single view and segment was used to estimate all strain values per patient.

To study the relationship of plaque insonification angles to the strain values, patients were divided into three categories. The first category comprised of patients with insonification angles less than five degrees (n=31), second category for angles between five to ten degrees (n=24) and finally a third category for angles greater than ten degrees (n=21). A qualitative representation of each category is presented later in the paper.

For a quantitative comparison of the strain indices derived from the five strain images, box and whisker plots are presented across the three different angle categories are presented. On each box, the median is indicated by the central mark, with the 25th and 75th percentiles denoted by the bottom and top edges of the box, respectively. The whiskers extend to the most extreme data points not considered outliers, and the outliers are plotted individually using the '+' symbol. Values that are 1.5 times the interquartile range away from the top or bottom of the box are considered outliers. A plot of axial strain vs maximum absolute principal strain and shear strain versus maximum shear strain is also plotted. The slopes estimated for the entire patient population and the three individual categories in these plots is quantified to examine if there is a difference in the slope estimated with insonification angles.

We also present vector image examples of plaques with their maximum principal strain and direction overlaid on the corresponding B-mode image to further understand the vector

principal strain distribution. The direction of the principal strain aligns with the direction of the Eigen vector corresponding to the Eigen value (principal strain). It is computed as:

$$\theta = \frac{\tan^{-1}\left(\frac{2\epsilon_{xy}^*}{\epsilon_{xx} - \epsilon_{yy}}\right)}{2}$$

where θ denotes the direction of the principal strain.

Lastly, to statistically examine if there are significant differences between strain indices estimated for the three angle categories, a Wilcoxon rank sum test was performed using MATLAB 2017 software on the difference between axial strain and maximum principal strain indices for the three angle categories. The same test was also performed on the difference between the shear strain and maximum shear strain.

Results

Figures 2, 3 and 4 present corresponding strain images on a human subject in each of the insonification angle category, i.e. below 5 degrees, angle between 5 to 10 degrees and angles above ten degrees respectively. Figure 2 presents a plaque with near wall angle of 0.25 degrees and far wall angle of 4.16 degrees. This plaque presented with lower axial strains when compared to lateral and shear strain. This is translated into principal strain derived values where we observe that the maximum absolute strain appears to have higher strain values in similar areas visualized on lateral and shear strain images. The maximum shear strain on the other hand closely follows the shear strain. Figure 3 presents plaque with a near wall angle 3.28 degrees and 7.67 degrees. Axial, lateral and shear strain in this case all have specific areas of high strain and the maximum absolute principal strain is also high in the same areas. Maximum shear strain follows a similar distribution as the shear strain but there are some new regions with high maximum shear strains, which did not exist in the corresponding shear strain image. Finally, figure 4 presents a plaque with a large insonification angle of 28.52 degrees. Again, the maximum absolute principal strain is high in the regions of high axial, lateral and shear strains while maximum shear strain follows a distribution similar to shear strain with some new additional regions of high strain.

Next, a quantitative comparison of each of the strain indices discussed above for the three angle categories is performed. Figures 5, 6 and 7 present box plots of AMS, MMS and MSD respectively for the five different strain images, respectively. The scale for the strain percentages are maintained the same for all plots for a given strain index for accurate comparisons and hence there are some outliers that were not depicted in the figures. Figure 5 demonstrates that for AMS, lateral strain indices have a lower median value than their axial counterparts. Higher shear strains are present when compared to axial and lateral strains. Shear strains also have a larger variation in values when compared to axial and lateral strains. Maximum shear strains present with a slightly higher median value but a similar variation in values when compared to shear strain. Maximum principal strain presents with the highest median value and the highest variation of all strain indices. However, no significant difference is observable between the angle groups shown in Figures 5a, 5b and

5c, respectively. Similar trends are seen in Figure 6 for MMS to those observed in figure 5 for AMS. Axial strain presented with a slightly higher median value compared to lateral strain and had a larger variation in values. Figure 7 demonstrates that for the MSD strain index, shear strain and maximum shear strain show very similar median values and variation. Axial strain again presented with more variation in its values when compared to lateral strain indices. Table 1 reports the median values of the strain indices plotted in Figures 5, 6 and 7. To summarize, median strain indices values from low to high were lateral, axial, shear, maximum shear and maximum principal across all angle groups.

Figure 8 plots axial strain versus maximum principal strain indices for AMS (figure 8a), MMS (figure 8b) and MSD (figure 8c). Figure 9 plots the same for shear strain versus maximum shear strain indices. The slopes and intercepts generated by linear regression are shown on the respective figures. From figure 8, it is observed that AMS and MMS present with a slope higher than one and a positive intercept while MSD presents with a slope very close to one and a positive intercept. Figure 9 demonstrates the same trends but with lower magnitudes for the slope and intercept for the shear versus maximum shear indices plot. The slopes and intercepts formed by individual angle groups are presented in Table 2.

Figure 10 presents vector images of maximum principal strain of the plaque presented in figure 3. Figure 10(a) presents the entire plaque while 10(b) and 10(c) present zoomed in views of the near and far wall plaque respectively. One in every thirty strain estimate is plotted as a vector for purpose of clear visualization. Similarly, figure 11 presents a vector image for plaque presented in figure 4. Here figure 11(b) and 11(c) present a zoomed in version of left and right regions of the plaque respectively.

Finally, statistical analysis with the Wilcoxon rank sum test is presented in Table 3. The p values for the test between any two groups did not reach significance.

Discussion

We can make the following observations from figures 5, 6 and 7 and Table 1. Strain indices derived from axial and lateral strain images presented with similar values. There were higher shear strain indices observed when compared to axial and lateral strain indices in all angle categories. Strain indices obtained from the maximum principal shear strain was slightly higher in magnitude when compared to axis-dependent shear strain. Strain indices derived from the maximum principal strain was higher than all the three axis dependent strain indices. The reason being that the maximum principal strain is along an axis orientation where the shear strain is zero. Hence the existing shear strains are incorporated into the maximum principal strain. This was also shown qualitatively in figures 2, 3 and 4, and is further demonstrated in Figures 8a and 8b where we have high slopes for axial strain versus maximum principal strain plots. Moreover, depending on if a given plaque region presents with higher lateral or axial strains, the maximum principal strain generally represents the strain distribution of the highest axis dependent component. Hence, it represents a “summed up” highest strain view of the plaque. Although this might be useful, it may not be sufficient to provide a complete diagnostic picture since each axis dependent strain may have its own

unique correlation to clinical significance. This information is lost when reporting using maximum principal strains as standalone strain indices.

Maximum shear strain on the other hand provides slightly higher and axis independent estimation of shear strain in plaque and can be used for quantifying the shear strains in plaque instead of the axis dependent shear strain without any negative consequences. An interesting observation from figure 9c is that some points are below the slope = 1 line indicating that the standard deviation was lower with the computation of the maximum shear strain perhaps due to plaque regions that were previously under estimated.

The angle dependence study is summarized in Table 2. For the strain indices AMS, and MMS the slope of the axial versus maximum principal strain line that does increase slightly with angle, however the y-intercept decreases with angle, which may in part be the reason for the slope increase. The shear versus maximum shear slopes and y-intercepts do not present with any trends. The MSD strain index presents a slope very close to 1 for both axial versus maximum principal and shear versus maximum shear strains. The former has a positive y-intercept while the latter does not.

Note also that the p values calculated using the Wilcoxon rank sum test between the three angle categories for the difference in the strain indices was not significant. The following may be the reasons why there is no significant difference. First, the number of patients in each group is small and may not be sufficient to reach significance. Second, although we tried to quantify a given plaque with one global angle, vessel tortuosity in the plaques may cause the angles to be locally different across the plaque. Finally, plaque is significantly heterogeneous, with blood flow not uniform or laminar across these stenotic and advanced atherosclerotic plaque patients and hence these variables have an effect on the principal strain indices along with plaque insonification angle.

The hypothesis that heterogeneity in plaque contributes to the principal strain direction can be further recognized from figures 10 and 11. Figure 10(b) with the smaller near wall plaque demonstrates a principal strain direction which is neither along the angle of insonification nor orthogonal to it but in a direction aligned to hemodynamic flow of the blood in the artery. Similarly, the far wall plaque in figure 10(c) show directions that vary in different regions but are fairly uniform in any given region of plaque. In figure 10(c) some directions are indeed along the angle of insonification but at the same time others are orthogonal to the insonification angle. Hence due to heterogeneity we visualize various angles and the average relationship with angle of insonification does not appear to be significant due to plaque heterogeneity. Similarly, figures 11(b) and 11(c) also show directions which vary across the plaque but are consistent along smaller plaque regions. Therefore, due to plaque heterogeneity, principal strain does not present with a direct linear relationship with angle of insonification.

In conclusion, we demonstrated that plaques have shear strains of slightly higher magnitude than axial and lateral strain. The maximum principal strain reports strain indices that are higher than individual axial, lateral and shear strain indices and the axial, lateral, and shear information is all incorporated into the maximum principal strain, which provides a net view

of the plaque but loses the information provided by individual direction dependent axial, lateral and shear strain. Maximum shear strain presents to be slightly higher but has similar values to that obtained for the axis dependent shear strain and may be a good measure for quantifying the shear strains in plaque. Plaques associated with advanced carotid atherosclerosis (60% or greater stenosis) also present with significant shearing strains; information which is lost when we compute principal strains which present a summed-up visualization of strains. Strain indices for different arterial insonification angles did not present with significant differences when compared to the axis dependent strain values and principal strain derived values which indicates that plaque heterogeneity may play a larger influence in determining the principal strain distribution than the angle of insonification in severely stenotic carotid plaque.

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References

- ACAS 1995 Endarterectomy for asymptomatic carotid artery stenosis JAMA 273 1421–8 [PubMed: 7723155]
- Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, Chiuve SE, Cushman M, Delling FN and Deo R 2018 Heart disease and stroke statistics—2018 update: a report from the American Heart Association Circulation 137 e67–e492 [PubMed: 29386200]
- Céspedes I, Huang Y, Ophir J and Spratt S 1995 Methods for estimation of subsample time delays of digitized echo signals Ultrason. Imaging 17 142–71 [PubMed: 7571208]
- Chaturvedi P, Insana MF and Hall TJ 1998 2-D companding for noise reduction in strain imaging IEEE transactions on ultrasonics, ferroelectrics, and frequency control 45 179–91
- Chen H and Varghese T 2009 Principal component analysis of shear strain effects Ultrasonics 49 472–83 [PubMed: 19201435]
- Dempsey RJ, Varghese T, Jackson DC, Wang X, Meshram NH, Mitchell CC, Hermann BP, Johnson SC, Berman SE and Wilbrand SM 2017 Carotid atherosclerotic plaque instability and cognition determined by ultrasound-measured plaque strain in asymptomatic patients with significant stenosis Journal of Neurosurgery 1–9
- Fekkes S, Saris AE, Menssen J, Nillesen MM, Hansen HH and de Korte CL 2018 Multi-Plane Ultrafast Compound 3D Strain Imaging: Experimental Validation in a Carotid Bifurcation Phantom Applied Sciences 8 637
- Fung-Kee-Fung S, Lee W-N, Ingrassia C, Costa K and Konofagou E Ultrasonics Symposium, 2005 IEEE, 2005), vol. Series 1): IEEE) pp 516–9
- Hansen HH, de Borst GJ, Bots ML, Moll FL, Pasterkamp G and de Korte CL 2016 Validation of noninvasive in vivo compound ultrasound strain imaging using histologic plaque vulnerability features Stroke 47 2770–5 [PubMed: 27686104]
- Huang C, He Q, Huang M, Huang L, Zhao X, Yuan C and Luo J 2017 Non-invasive identification of vulnerable atherosclerotic plaques using texture analysis in ultrasound carotid elastography: An in vivo feasibility study validated by magnetic resonance imaging Ultrasound Med. Biol 43 817–30 [PubMed: 28153351]
- Huang C, Pan X, He Q, Huang M, Huang L, Zhao X, Yuan C, Bai J and Luo J 2016 Ultrasound-Based Carotid Elastography for Detection of Vulnerable Atherosclerotic Plaques Validated by Magnetic Resonance Imaging Ultrasound Med. Biol 42 365–77 [PubMed: 26553205]

- Korukonda S, Nayak R, Carson N, Schifitto G, Dogra V and Doyley MM 2013 Noninvasive vascular elastography using plane-wave and sparse-array imaging IEEE transactions on ultrasonics, ferroelectrics, and frequency control 60 332–42
- Langsfeld M, Gray-Weale AC and Lusby RJ 1989 The role of plaque morphology and diameter reduction in the development of new symptoms in asymptomatic carotid arteries J. Vasc. Surg 9 548–57 [PubMed: 2651727]
- Lee W-N, Qian Z, Tosti CL, Brown TR, Metaxas DN and Konofagou EE 2008 Preliminary validation of angle-independent myocardial elastography using MR tagging in a clinical setting Ultrasound Med. Biol 34 1980–97 [PubMed: 18952364]
- Li RX, Apostolakis IZ, Kemper P, McGarry MD, Ip A, Connolly ES, McKinsey JF and Konofagou EE 2019 Pulse Wave Imaging in Carotid Artery Stenosis Human Patients in Vivo Ultrasound Med. Biol 45 353–66 [PubMed: 30442386]
- Lopata RG, Nillesen MM, Hansen HH, Gerrits IH, Thijssen JM and De Korte CL 2009 Performance evaluation of methods for two-dimensional displacement and strain estimation using ultrasound radio frequency data Ultrasound Med. Biol 35 796–812 [PubMed: 19282094]
- McCormick M, Rubert N and Varghese T 2011 Bayesian regularization applied to ultrasound strain imaging IEEE Trans. Biomed. Eng 58 1612–20 [PubMed: 21245002]
- McCormick M, Varghese T, Wang X, Mitchell CC, Kliewer M and Dempsey RJ 2012 Methods for robust in vivo strain estimation in the carotid artery Phys. Med. Biol 57 7329 [PubMed: 23079725]
- McCormick MM and Varghese T 2013 An approach to unbiased subsample interpolation for motion tracking Ultrason. Imaging 35 76–89 [PubMed: 23493609]
- Mercure E, Destrepes F, Cardinal M-H R, Porée J, Soulez G, Ohayon J and Cloutier G 2014 A local angle compensation method based on kinematics constraints for non-invasive vascular axial strain computations on human carotid arteries Comput. Med. Imaging Graph 38 123–36 [PubMed: 24050884]
- Meshram N, Jackson D, Varghese T, Mitchell C, Wilbrand S, Dempsey R and Hermann B 2019 A Cross-Sectional Investigation of Cognition and Ultrasound-Based Vascular Strain Indices Arch. Clin. Neuropsychol
- Meshram NH and Varghese T 2018 GPU Accelerated Multilevel Lagrangian Carotid Strain Imaging IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control 65 1370–9
- Meshram NH, Varghese T, Mitchell CC, Jackson DC, Wilbrand SM, Hermann BP and Dempsey RJ 2017 Quantification of carotid artery plaque stability with multiple region of interest based ultrasound strain indices and relationship with cognition Phys. Med. Biol 62 6341–60 [PubMed: 28594333]
- Naim C, Cloutier G, Mercure E, Destrepes F, Qin Z, El-Abyad W, Lanthier S, Giroux M-F and Soulez G 2013 Characterisation of carotid plaques with ultrasound elastography: feasibility and correlation with high-resolution magnetic resonance imaging Eur. Radiol 23 2030–41 [PubMed: 23417249]
- NASCET 1999 The North American symptomatic carotid endarterectomy trial surgical results in 1415 patients Stroke 30 1751–8 [PubMed: 10471419]
- Nayak R, Huntzicker S, Ohayon J, Carson N, Dogra V, Schifitto G and Doyley MM 2017 Principal strain vascular elastography: Simulation and preliminary clinical evaluation Ultrasound Med. Biol 43 682–99 [PubMed: 28057387]
- Nayak R, Schifitto G and Doyley MM 2018 Visualizing angle-independent principal strains in the longitudinal view of the carotid artery: Phantom and in vivo evaluation Ultrasound Med. Biol 44 1379–91 [PubMed: 29685590]
- Ophir J, Cespedes I, Ponnekanti H, Yazdi Y and Li X 1991 Elastography: a quantitative method for imaging the elasticity of biological tissues Ultrason. Imaging 13 111–34 [PubMed: 1858217]
- Porée J, Garcia D, Chayer B, Ohayon J and Cloutier G 2015 Noninvasive vascular elastography with plane strain incompressibility assumption using ultrafast coherent compound plane wave imaging IEEE Trans. Med. Imaging 34 2618–31 [PubMed: 26625341]
- Ribbers H, Lopata RG, Holeyijn S, Pasterkamp G, Blankensteijn JD and De Korte CL 2007 Noninvasive two-dimensional strain imaging of arteries: validation in phantoms and preliminary experience in carotid arteries in vivo Ultrasound Med. Biol 33 530–40 [PubMed: 17280769]

- Roy Cardinal M-H, Heusinkveld MH, Qin Z, Lopata RG, Naim C, Soulez G and Cloutier G 2017 Carotid artery plaque vulnerability assessment using noninvasive ultrasound elastography: Validation with MRI American journal of Roentgenology 209 142–51 [PubMed: 28639927]
- Salem M, Bown M, Sayers R, West K, Moore D, Nicolaides A, Robinson T and Naylor A 2014 Identification of patients with a histologically unstable carotid plaque using ultrasonic plaque image analysis Eur. J. Vasc. Endovasc. Surg 48 118–25 [PubMed: 24947079]
- Shi H, Mitchell CC, McCormick M, Kliewer MA, Dempsey RJ and Varghese T 2008 Preliminary in vivo atherosclerotic carotid plaque characterization using the accumulated axial strain and relative lateral shift strain indices Phys. Med. Biol 53 6377 [PubMed: 18941278]
- Shi H and Varghese T 2007 Two-dimensional multi-level strain estimation for discontinuous tissue Phys. Med. Biol 52 389 [PubMed: 17202622]
- Varghese T 2009 Quasi-static ultrasound elastography Ultrasound clinics 4 323–38 [PubMed: 20798841]
- Varghese T, Meshram NH, Mitchell CK, Hermann BP, Wilbrand SM, Jackson DC and Dempsey RJ 2017 IEEE International Ultrasonics Symposium (IUS), 2017, vol. Series: IEEE pp 1–4
- Varghese T and Ophir J 1997 Enhancement of echo-signal correlation in elastography using temporal stretching IEEE transactions on ultrasonics, ferroelectrics, and frequency control 44 173–80
- Wang X, Jackson DC, Mitchell CC, Varghese T, Wilbrand SM, Rocque BG, Hermann BP and Dempsey RJ 2016 Classification of Symptomatic and Asymptomatic Patients with and without Cognitive Decline Using Non-Invasive Carotid Plaque Strain Indices as Biomarkers Ultrasound Med. Biol 42 909–18 [PubMed: 26778288]
- Wang X, Jackson DC, Varghese T, Mitchell CC, Hermann BP, Kliewer MA and Dempsey RJ 2014 Correlation of cognitive function with ultrasound strain indices in carotid plaque Ultrasound Med. Biol 40 78–89 [PubMed: 24120415]
- Zervantonakis I, Fung-Kee-Fung S, Lee W and Konofagou E 2007 A novel, view-independent method for strain mapping in myocardial elastography: eliminating angle and centroid dependence Phys. Med. Biol 52 4063 [PubMed: 17664595]

Figure 1:
Example of identifying wall side points of plaque to calculate the angle of plaque

Figure 2:

A plaque with near wall angle of 0.25 degrees and far wall angle of 4.16 degrees (a) segmented plaque mesh, (b) Axial strain, (c) Lateral Strain, (d) Shear Strain, (e) Max. Abs. Principal Strain and (f) Max. Shear Strain

Figure 3:
A plaque with near wall angle of 3.28 degrees and far wall angle of 7.67 degrees (a) segmented plaque mesh, (b) Axial strain, (c) Lateral Strain, (d) Shear Strain, (e) Max. Abs. Principal Strain and (f) Max. Shear Strain

Figure 4: A plaque with far wall angle of 28.52 degrees (a) segmented plaque mesh, (b) Axial strain, (c) Lateral Strain, (d) Shear Strain, (e) Max. Abs. Principal Strain and (f) Max. Shear Strain

Figure 5-

Mean of strain values over entire plaque averaged for an entire cardiac cycle, Average Mean Strain(AMS). (a) plaque angled less than five degrees (n=31) (b) plaque angled between five to ten degrees (n=24) (c) plaque angled above ten degrees (n=21)

Figure 6-

Maximum of the mean of strain values over entire plaque over an entire cardiac cycle, Maximum Mean Strain (MMS). (a) plaque angled less than five degrees (n=31) (b) plaque angled between five to ten degrees (n=24) (c) plaque angled above ten degrees (n=21)

Figure 7-
Standard deviation of strain values over entire plaque averaged over an entire cardiac cycle, Mean Standard deviation(MSD) (a) plaques angled less than five degrees (n=31) (b) plaque angled between five to ten degrees (n=24) (c) plaque angled above ten degrees (n=21)

Figure 8:

Axial Strain vs. Max Principal Strain for (a) Average Mean Strain (AMS), (b) Maximum Mean Strain (MMS) and (c) Mean Standard deviation (MSD)

Figure 9:

Shear Strain vs. Max. Shear Strain for (a) Average Mean Strain (AMS). (b) Maximum Mean Strain (MMS) and (c) Mean Standard deviation (MSD)

Figure 10: Maximum principal strain with vector directions of plaque presented in figure 3, (a) entire plaque, (b) Zoomed in on near wall, (c) zoomed in on far wall

Figure 11: Maximum principal strain with vector directions of plaque presented in figure 4, (a) entire plaque, (b) Zoomed in on left side, (c) zoomed in on right side

Table 1:

Median Strain Values

	Angle (degrees)	Axial	Lateral	Shear	Max. Prin.	Max. Shear
AMS	less than 5	2.14	1.77	4.30	6.70	5.02
	5 to 10	2.56	2.25	4.28	6.45	4.93
	greater than 10	2.21	1.96	2.91	5.64	4.02
MMS	less than 5	3.12	2.68	5.83	9.12	7.08
	5 to 10	3.59	2.66	5.40	9.15	6.60
	greater than 10	3.32	3.28	4.64	8.55	5.76
MSD	less than 5	1.96	1.52	3.12	3.82	3.09
	5 to 10	2.77	2.02	3.34	4.31	3.22
	greater than 10	2.00	1.41	2.49	3.19	2.43

Table 2:

Slopes across angles for the three strain indices

	Angle (degrees)	Axial vs Max. Prin.			Shear vs Max. Shear		
		slope	y-intercept	R ²	slope	y-intercept	R ²
AMS	less than 5	1.57	2.79	0.85	1.20	-0.14	0.95
	5 to 10	1.60	2.20	0.87	1.12	0.50	0.97
	greater than 10	1.79	1.64	0.85	1.22	0.03	0.97
MMS	less than 5	1.37	4.40	0.75	1.23	-0.37	0.93
	5 to 10	1.49	3.09	0.86	1.11	0.84	0.97
	greater than 10	2.06	1.26	0.84	1.19	0.07	0.97
MSD	less than 5	0.96	1.85	0.78	1.04	-0.14	0.98
	5 to 10	1.05	1.68	0.77	1.04	-0.03	0.97
	greater than 10	1.01	1.37	0.71	0.98	0.07	0.96

Table 3:

P values with Wilcoxon test for difference in axial and maximum principal strain, shear and max shear strain between the three angle groups. p_{12} is between angles below 5 and angles 5 to 10, p_{13} is between angles below 5 and angles above 10 and p_{23} is between angles 5 to 10 and angles above 10 degrees.

	diff (Axial, Max. Prin.)			diff (Shear, Max. Shear)		
	p_{12}	p_{13}	p_{23}	p_{12}	p_{13}	p_{23}
AMS	0.67	0.26	0.50	0.12	0.35	0.47
MMS	0.51	0.36	0.88	0.07	0.58	0.27
MSD	0.62	0.51	0.81	0.49	0.88	0.47