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Correlation of Cognitive Function with Ultrasound Strain Indices in Carotid Plaque

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Abstract

Instability in carotid vulnerable plaque can generate cerebral microemboli, that may be related to both stroke and eventual cognitive abnormality. Strain imaging to detect plaque vulnerability based on regions with large strain fluctuations, with arterial pulsation, may be able to determine risk of cognitive impairment. Plaque instability may be characterized by increased strain variations over a cardiac cycle. Radiofrequency signals for ultrasound strain imaging were acquired from the carotid arteries of 24 human subjects using a Siemens Antares with a VFX 13-5 linear array transducer. These patients underwent standardized cognitive assessment (Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)). Plaque regions were segmented by a radiologist at end-diastole using the Medical Imaging Interaction Toolkit. A hierarchical block-matching motion tracking algorithm was utilized to estimate the cumulated axial, lateral, and shear strains within the imaging plane. The maximum, minimum and peak-to-peak strain indices in the plaque computed from the mean cumulated strain over a small region of interest in the plaque with large deformations, were obtained. The maximum and peak-to-peak mean cumulated strain indices over the entire plaque region were also computed. All the strain indices were then correlated with RBANS Total performance. Overall cognitive performance (RBANS Total) was negatively associated with values of the maximum strain and the peak-to-peak for axial and lateral strains respectively. There was no significant correlation between the RBANS Total score and shear strain, and strain indices averaged over the entire identified plaque for this group of patients. However, correlation of the maximum lateral strain was higher for symptomatic patients ($r = -0.650$, $p = 0.006$) than that for asymptomatic patients ($r = -0.115$, $p = 0.803$). On the other hand correlation for maximum axial strain averaged over the entire plaque region was significantly higher for asymptomatic patients ($r = -0.817$, $p = 0.016$) than that for symptomatic patients ($r = -0.224$, $p = 0.402$). The results reveal a direct relationship between the maximum axial and lateral strain indices in carotid plaque with cognitive impairment.

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Keywords

Elastography; elasticity imaging; carotid plaque; motion tracking; multi-level; displacement; strain; vascular cognitive dementia

Introduction

Carotid plaque and possible embolic stroke are strongly linked through emboli generated by plaque rupture. Vulnerable plaques are unstable and can be an origination point for emboli. It is possible that plaque vulnerability is enhanced when the plaque undergoes significant strain variations over the arterial pulsation of the cardiac cycle. Emboli can flow into the vasculature of the brain and can cause ischemic events resulting in stroke, vascular cognitive impairment or both (Whisnant et al. 1990). For every patient suffering a stroke, twice as many people will experience vascular cognitive impairment (Hachinski et al. 2006). There is evidence that cerebral emboli have a significant correlation with dementia and are associated with a faster decline of cognitive function (Purandare et al. 2006; Purandare et al. 2007). It has also been suggested that increased strain in plaque may correlate with cognitive abnormalities (Rocque et al. 2012), suggesting that it is important to identify patients with vulnerable plaques to help prevent future stroke and cognitive impairment.

Characterization of carotid plaque plays an important role in detecting the plaque vulnerability to rupture. Ultrasound is a noninvasive option for imaging superior shallow vessels such as the carotid artery. B-mode images are commonly used clinically, but they are not sufficient to identify the vulnerability of plaque since they can only separate plaque from normal tissue; but it is difficult to differentiate thrombus from surrounding lipidic plaque (Noritomi et al. 1997b). Quantitative ultrasound (QUS) has been used to assess acoustic properties of tissue, such as the attenuation coefficient and integrated backscatter, since differences in acoustic properties may reflect differences in tissue composition (Picano et al. 1985; Barzilai et al. 1987; Wilson et al. 1994; Bridal et al. 1997b; Bridal et al. 1997a; Noritomi et al. 1997a; Noritomi et al. 1997b; Roth et al. 1997; Lee et al. 1998; Bridal et al. 2000; Shi et al. 2008b; Shi et al. 2009). Nair et al. (2004) built a classification tree model for autoregressive spectral analysis and developed a real-time automated tissue characterization approach using IVUS images on coronary plaques. Their results correspond well with histology classifications and have potential for virtual histology evaluations and plaque vulnerability assessments (Nair et al. 2001; Nair et al. 2002; Nair et al. 2004).

Ultrasound strain imaging (Ophir et al. 1991) can be utilized to estimate the mechanical deformation of plaque, and can therefore assist in the characterization of plaque vulnerability (Varghese 2009). Most of the research on plaque characterization has focused on intravascular ultrasound (IVUS) because of its high spatial resolution. Intravascular elastography has been shown to identify vulnerable plaque both *in vitro* and *in vivo*. Fibrous tissue has lower mean radial strain (0 – 0.2%) than lipidic tissue (1 – 2%) (de Korte et al. 1998; de Korte et al. 2000a; de Korte et al. 2000b; de Korte and van der Steen 2002). Schaar et al. (2003) used strain imaging and histology separately to identify vulnerable plaque, and plotted strain values against histology indices. They showed intravascular elastography to be a good diagnostic tool due to the high sensitivity of 88% and 89% specificity using a receiver operator characteristic (ROC) analysis for a strain threshold of 1.26% (Schaar et al. 2003).

There are fewer studies of noninvasive carotid plaque imaging using elastography, and strain imaging (Maurice et al. 2004; Maurice et al. 2005; Ribbers et al. 2007; Schmitt et al. 2007; Shi and Varghese 2007; Maurice et al. 2008; Shi et al. 2008a; Hansen et al. 2009; Hansen et

al. 2010; McCormick et al. 2011; Idzenga et al. 2012; McCormick et al. 2012). Maurice et al. (2004) proposed a Von Mises parameter to characterize vessel wall and utilized a Lagrangian speckle model estimator to calculate the strain tensor in order to estimate axial, lateral, shear and radial strain in the plaque. They indicated their method to be reproducible, since the correlation of strain values between left and right common carotid arteries was significant. Schmitt et al. (2007) implemented the Lagrangian model to estimate strain tensors on both cross-sectional and longitudinal imaging views. They found that axial strain and axial shear strain can provide plaque size information, along with composition and mechanical properties. Ribbers et al. (2007) calculated the radial and circumferential strain in two ways; from axial and shear strain and from principle strain. The strain patterns obtained agree with theory, but zero-strain zones exist at diagonal boundaries. Hansen et al. (2010) improved this technique and was able to use an angle-compounding technique to reduce noise artifacts to obtain better radial and circumferential strain estimations from only axial strain. Since ultrasound beams align with the axial direction, it is natural to study the plaque in a longitudinal imaging plane. Idzenga et al. (2012) were able to examine the longitudinal shear strain in carotid artery utilizing radiofrequency (RF) data instead of B-mode data. Shi et al. (2008a) developed a multi-level tracking algorithm to calculate displacement and strain and indicated that axial strain and lateral displacement can separate soft from calcified plaque. They therefore hypothesized that this differentiation could help identify vulnerable plaque using cumulated strain indices. McCormick et al. (2012) developed a strain estimation algorithm based on a hierarchical framework utilizing Bayesian regularization to estimate all components of the strain tensor and found that the strain quantities derived from the strain tensor are capable of quantifying vulnerability of carotid plaque based on cumulated strain indices.

In this paper, we utilize the algorithms developed by our group to evaluate the distribution and variation of axial, lateral and shear strains for *in vivo* carotid plaque. We focus on the correlation between cognitive function and multiple strain indices.

Materials and method

Data acquisition

Ultrasound imaging was performed on 24 patients, scheduled for a carotid endarterectomy procedure (CEA), and presented with significant plaque. Patients provided informed consent using a protocol approved by the University of Wisconsin-Madison Institutional Review Board (IRB) prior to the ultrasound and strain imaging study. The patients ranged in age from 44 to 79, with a mean and standard deviation of 65.88 ± 8.74 respectively. These patients then underwent CEA at the University of Wisconsin-Madison Hospitals and Clinics. Additional details on the patients and the different measurements are presented in Table 1.

RF echo signal data, along with clinical B-mode images and color-flow Doppler images, were acquired using a Siemens Antares ultrasound system (Siemens Ultrasound, Mountain View, CA, USA) equipped with a VFX 13-5 linear transducer. The transmit frequency of the transducer was set to 11.4 MHz with a single transmit focus set at the depth of plaque. The total depth of the B-mode image was 4 cm, and 508 A-lines in the lateral direction, with a total field lateral width of 38 mm was acquired. RF data was digitized at a 40 MHz sampling frequency. At least two cardiac cycles of RF data were obtained.

Plaque regions were segmented by a radiologist at end-diastole using the Medical Imaging Interaction Toolkit (MITK). Two complete cardiac cycles were chosen, with plaque segmentation performed on the three end-diastolic frames. The plaque regions were segmented on the B-mode images constructed from RF data, as shown in Figure 1. Clinical B-mode and color-flow Doppler images were also used by the radiologist to better define the

plaque borders. The plaque dimension reported in Table 1 was measured by averaging the area of the segmented region over the three end-diastolic frames.

The 24 patients were classified as either symptomatic, asymptomatic or questionable based on clinical findings. A patient was classified as symptomatic if he or she presented with stroke or a transient ischemic attack (TIA), and was deemed asymptomatic otherwise. Carotid stenosis and indication for CEA for asymptomatic patients were based on other clinical symptoms or imaging studies performed; for example on patients presenting with cardiac conditions. Patients underwent objective cognitive assessment using a mental status screening measure (Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)) which provides an index of overall cognitive status as well as five indices for specific cognitive abilities (Immediate Memory, Visuospatial/Constructional, Language, Attention, and Delayed Memory) (Randolph et al. 1998). All index scores are age-adjusted and normalized (Duff et al. 2003). Plaque assessment using B-mode and strain imaging was conducted while blinded to the cognitive results. To reduce the number of comparisons only the RBANS Total score was used to compare with all strain indices with a significance level of $p < 0.05$ using a t -test.

Strain indices estimation

A hierarchical block-matching motion tracking algorithm developed in our laboratory (McCormick et al. 2012), was utilized. Block matching between pre- and post-deformation frames was performed using a hierarchical framework and normalized cross-correlation analysis performed over three iterations (McCormick et al. 2011). The matching block was 15×28 pixels at the top level, and 10×18 pixels at the bottom level. There was no overlap between the blocks. On the axial direction one pixel represents 0.02mm, while on the lateral direction one pixel represents 0.075mm. A dynamic frame skip method was utilized to obtain high quality motion tracking with a short frame skip during systole and a long frame skip during end diastole. Incremental local displacements were tracked, estimated and then filtered with a 3×3 pixel median filter to remove outliers. Local strain was then assessed by applying a least-squares gradient over a 3×3 pixel radius from displacement estimation and accumulated over a cardiac cycle using the end-diastolic frame as the reference frame.

We utilized this method to estimate the accumulated axial, lateral, and shear strain distribution in plaques identified within the imaging plane. Shear strain was defined by the

expression
$$e_{xy} = \frac{1}{2} \left(\frac{\partial d_y}{\partial x} + \frac{\partial d_x}{\partial y} \right)$$
, where x and y represent the lateral and axial directions respectively (McCormick et al. 2012). Strain images were computed inside the segmented plaque and overlaid on the B-mode images. Displacement and strain between consecutive frames calculated by block-matching motion tracking algorithm were relatively small since the frame rates we used were no less than 27 fps. We present accumulated strain indices over a cardiac cycle to better characterize the elasticity of plaque tissue.

From the accumulated strain calculated in each subsequent frame, a small region of interest (ROI) in the plaque with maximum strain was found. We limited this area to be within a 10 – 20 data points range around the center of the ROI. The maximum strain of the selected plaque ROI in each frame was then obtained by averaging the strain values in this small ROI to reduce noise. The corresponding minimum and peak-to-peak strain indices in the same ROI were also computed, as was the mean strain over the entire plaque. From the mean strains over two cardiac cycles, we estimated the maximum, minimum and peak-to-peak strain indices over the entire plaque region. Strain indices were then correlated with RBANS Total scores using Pearson's correlation coefficients.

Results

Figure 2 (a) shows a typical axial strain image for the plaque demarcated in Fig. 1. The axial strain magnitude and direction are depicted on the color bar overlaid on the gray-scale B-mode images. Axial strains were averaged in the small ROI and over the entire plaque, respectively. The mean axial strains and standard deviation (STD) are plotted in Fig. 2 (b) and (c). The strain curves depict the deformation over two cardiac cycles. The variation in the strain over the two cardiac cycles are not identical, as shown in Fig. 2 (b), because of the irregular and turbulent flow patterns caused by the stenosis in the vessel due to the presence of plaque. Note that the mean axial strain computed over the entire plaque is significantly lower than that obtained within the small ROI. On the other hand, the STD over the entire plaque is much higher than that in the small ROI. This suggests that in this heterogeneous plaque, the axial strain estimate varies significantly. The maximum axial strain can get as high as 11%, but the mean peak axial strain is around 3%.

In a similar manner, the variability in the lateral strain in the same plaque is shown in Figure 3. The lateral strain presents similar trends; in that it varies significantly inside the plaque so the mean value is much smaller, with a peak value of 2% compared to the maximum lateral strain of 9% in a small ROI, and the STD is also larger, as expected. The distribution of lateral strain inside the plaque suggests that the composition of plaque changes from region to region.

Finally the shear strain in the same plaque is shown in Figure 4. The mean shear strain of the entire plaque does not exhibit a cyclic behavior, when compared to axial and lateral strain estimates. The mean peak shear strain is only 1%, but the maximum shear strain in the ROI is around 15%. Observe that the variation in the shear strain is quite similar to that of the axial and lateral strain. The behavior of the three strain indices indicate the variability in the strain estimates over different types of tissue within a single plaque. Since the mean strain in the small ROI has a lower standard deviation, we consider the maximum strain averaged over the small ROI to be the maximum strain value within the entire plaque.

The maximum, minimum and peak-to-peak strain indices over a small ROI with the largest deformation were then obtained from the mean strain value in the ROI. The legend identifying the plots and data points for figures 6–figure 10 is shown in Figure 5. Figure 6 presents a plot of RBANS Total score versus axial strain indices. As shown in Table 1, 16 out of 24 patients were identified as symptomatic, 7 were asymptomatic and 1 was questionable. A linear fit was performed for symptomatic, asymptomatic and for all the patients respectively to show the correlation of the two variables. The strains shown in the plots are all scalar values; the maximum strain is always positive and the minimum strain is always negative. For better comparison, we use absolute value for the minimum axial strain values so all the indices are positive. The Pearson's coefficient (r) and the significance value (p) were also calculated for each correlation. Overall the RBANS Total score appears lower with increasing strain indices. The maximum and peak-to-peak axial strain, also reveal a correlation to RBANS Total score. The correlation or linear fit between the RBANS score for asymptomatic and symptomatic is higher or improved within the ROI. However, the correlation of absolute minimum strain is weaker than the other two indices.

The association of RBANS Total score with the lateral strain indices is depicted in Figure 7 where a negative correlation between cognition and the strain indices is observed. The maximum and peak-to-peak lateral strain correlated significantly with cognition. Although the absolute minimum lateral strain shows a weaker correlation, it is not as weak as the absolute minimum axial strain. Note that the association between cognition and strain is

higher for strains within the ROI, however we observe a decrease in the correlation with asymptomatic patients, along with a change in the correlation to a positive value.

Figure 8 demonstrates similar correlations with shear strain indices. Note that the correlation is much weaker for shear strain indices than the axial and lateral strain indices. The absolute minimum shear strain reveals a positive correlation with RBANS Total score, as opposed to the negative correlations observed for the entire patient group for axial and lateral strain indices.

Observe from these plots that the correlation of the RBANS Total score to absolute minimum strain in the ROI is rather weak. Therefore only the maximum and peak-to-peak mean strain over the entire plaque region was computed, in the rest of the plots. The linear correlation between RBANS Total score with maximum mean strain indices over the entire plaque is shown in Figure 9, while the peak-to-peak mean strain indices are shown in Figure 10. Note that when the strain estimates are averaged over the entire plaque region, the maximum and peak-to-peak axial strain shows only a weak correlation with RBANS Total score for all patients. Note that the linear fits for the symptomatic patients generally follow the trend, and dominates the results for the entire group of patients for the axial and shear strain indices. However, we do observe significant deviations between the symptomatic and asymptomatic patients for the linear fit for the lateral strain indices; but the correlation is rather weak.

Overall, the mean strain indices for the 7 asymptomatic patients are slightly higher than that for the 16 symptomatic patients, and the mean RBANS score for the asymptomatic group is also lower than that for the symptomatic group. From the figures, we observe that there is no significant correlation between the RBANS Total score and strain indices averaged over the entire plaque region. However, the maximum and peak-to-peak axial and lateral strain show some correlation with an r value around 0.5, and a significant p -value of less than 0.05. For the symptomatic group, the correlation for maximum and peak-to-peak strain indices is higher. However, the correlation for strain indices averaged over the entire plaque region is significantly higher for asymptomatic group.

Discussion

In this paper we have shown that a relationship exists between cognitive function and the maximum and peak-to-peak axial and lateral strain indices. As the axial and lateral strain indices increase in plaque, there appears to be a corresponding poorer performance in the cognitive function for these patients. Since these strain indices primarily indicate the extent of deformation of plaque based on pulsatile flow in the carotid over the cardiac cycle, where larger deformations point to the presence of areas of softer plaques or variability in plaque composition over its length, larger deformations may therefore indicate an increased probability of plaque rupture in these softer plaques. Deformation of the carotid wall and plaque is caused by a combination of wall shear stress, wall tensile stress and cyclic force induced by the pulsatile blood pressure (Richardson et al. 1989; van der Wal and Becker 1999; Lee 2000; Gao and Long 2008). The buildup of plaque disrupts blood flow and results in hemodynamic changes such as high velocity jets that introduce shear stresses and turbulence which lead to blood pressure fluctuations over the length of the blood vessel (DePaola et al. 1992; Slager et al. 2005; Kefayati and Poepping 2013). Re-circulating flow, high shear stresses and increasing turbulence in turn can accelerate plaque rupture (Stein and Sabbah 1974; Loree et al. 1991; Reininger et al. 1995; Bluestein et al. 1997; Poepping et al. 2010). As a consequence of plaque rupture, microemboli or even emboli may flow into the brain and cause ischemic events leading to stroke or vascular dementia, which may result in

or be accompanied by cognitive impairment. This study helps establish the relationship between increasing strain indices in plaque and cognitive impairment through embolism.

Previous studies have shown that lateral strain estimation incurs more noise artifacts than axial strain because of the relative small dimensions of the plaque when compared to the lateral resolution of ultrasound system and their heterogeneous nature (Shi et al. 2008a). Shear strains, may therefore, include artifacts since it is neither aligned nor perpendicular to the ultrasound beam. This may explain the absence of a cyclic trend with the shear strain over a cardiac cycle. Axial strain indices overall provide the best correlation with RBANS Total score. Our improved algorithm allows for better tracking of the lateral deformation and thereby lateral strain estimation (McCormick et al. 2012). Lateral strain indices obtained using this algorithm, also show improved correlation with the RBANS Total score, although the correlation is not as good as that obtained using the axial strain indices as expected. The fact that lateral strain indices also show strong correlations with RBANS score especially for symptomatic patients indicate the utility of using lateral strains in this paper.

Most plaques are heterogeneous and difficult to completely classify as either soft or calcified. Plaque stiffness variations, however, can be evaluated by the distribution of local axial and lateral strains within the plaque, from the estimated strain images. These stiffness variations suggest that regions with highest strains (maximum values) or deformations may tend to break off and detach from the rest of plaque. Due to heterogeneity, a plaque with lower mean strain values can still possess localized regions with very high strain, that may be prone to rupture. The lack of significant correlation between the RBANS Total score with strain indices averaged over the entire plaque region, could therefore be due to local strain estimates from the small pockets of softer plaque embedded in large heterogeneous plaque regions, being averaged out over the entire plaque.

Note that the correlation of maximum and peak-to-peak lateral strain to RBANS Total score is much higher for symptomatic patients, but weak for asymptomatic patients. The comparison of symptomatic and asymptomatic patients brings up a possible hypothesis, indicating that the rupture of carotid plaque for symptomatic patients may have already occurred with ongoing emboli, whereas for asymptomatic patients, the plaque is still intact. We hypothesize that ruptured plaque, tend to have larger deformations in the lateral direction due to the possible fissures in plaque after rupture. On the other hand, for intact plaques, the fibrous cap may limit the lateral deformation of the entire plaque. However, lipidic regions within these plaques may break off and generate emboli eventually. This is consistent with our observation that asymptomatic patients have slightly higher axial than lateral strains within the plaque. Note the high correlation between RBANS Total score and axial strain indices averaged over the entire plaque region for asymptomatic patients, which are significantly higher. The RBANS correlation with the lateral strains indices for these patients are however significantly lower.

Since both symptomatic and asymptomatic patients were studied, the relationship between cognitive impairment and characterization of plaque may lead to further investigation of these patient groups. In addition to clinically recognized stroke, “silent” strokes may occur, and are five times more prevalent (Vermeer et al. 2003). Silent strokes are not detected based on classical transient ischemic attack (TIA) symptoms and therefore difficult to prevent. It is likely that these “silent” strokes may be causing accumulated cognitive decline. Studies have suggested that silent stroke occurs with concurrent subclinical emboli (Dempsey et al. 2010) and is better understood with cognitive impairment studies (Elias et al. 2004). This is consistent with our study that some of the asymptomatic patients may have great potential of developing emboli. Thus ultrasound strain imaging may be a surrogate in the clinic to detect the potential risk of having a silent stroke.

Despite the relationship described in this paper, examination of a larger number of patients is required to further establish the correlation. Note that the correlation not being significant for the asymptomatic patients may also be due to the small sample size. In addition, the blood pressure for patients was not documented in our study. More detailed analysis of the different RBANS components may also be enlightening, for example, the correlation of each of the index scores in RBANS to the strain indices.

Conclusion

In summary, the results reveal a significant relationship between the maximum and peak-to-peak axial and lateral strain indices in carotid plaque with cognitive function. Since ultrasound strain indices may assist in the identification of plaques prone to rupture, which in turn causes emboli, it plays an important role in characterizing plaque and detecting vulnerability of plaque. This correlation study indicates that these microemboli may be related to cognitive impairment. While silent stroke is strongly linked with cognitive impairment, it suggests that ultrasound strain imaging can play an important role in predicting embolism and preventing potential silent strokes.

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References

- Barzilai B, Saffitz JE, Miller JG, Sobel BE. Quantitative ultrasonic characterization of the nature of atherosclerotic plaques in human aorta. *Circ Res.* 1987; 60:459–463. [PubMed: 3555884]
- Bluestein D, Niu L, Schoepfoerster RT, Dewanjee MK. Fluid mechanics of arterial stenosis: relationship to the development of mural thrombus. *Ann Biomed Eng.* 1997; 25:344–356. [PubMed: 9084839]
- Bridal SL, Beyssen B, Fornes P, Julia P, Berger G. Multiparametric attenuation and backscatter images for characterization of carotid plaque. *Ultrason Imaging.* 2000; 22:20–34. [PubMed: 10823495]
- Bridal SL, Fornes P, Bruneval P, Berger G. Correlation of ultrasonic attenuation (30 to 50 MHz and constituents of atherosclerotic plaque. *Ultrasound Med Biol.* 1997a; 23:691–703. [PubMed: 9253817]
- Bridal SL, Fornes P, Bruneval P, Berger G. Parametric (integrated backscatter and attenuation) images constructed using backscattered radio frequency signals (25–56 MHz) from human aortae in vitro. *Ultrasound Med Biol.* 1997b; 23:215–229. [PubMed: 9140180]
- de Korte CL, Pasterkamp G, van der Steen AF, Woutman HA, Bom N. Characterization of plaque components with intravascular ultrasound elastography in human femoral and coronary arteries in vitro. *Circulation.* 2000a; 102:617–623. [PubMed: 10931800]
- de Korte CL, van der Steen AF. Intravascular ultrasound elastography: an overview. *Ultrasonics.* 2002; 40:859–865. [PubMed: 12160059]
- de Korte CL, van der Steen AF, Cepedes EI, Pasterkamp G, Carlier SG, Mastik F, Schoneveld AH, Serruys PW, Bom N. Characterization of plaque components and vulnerability with intravascular ultrasound elastography. *Phys Med Biol.* 2000b; 45:1465–1475. [PubMed: 10870704]
- de Korte CL, van der Steen AF, Cespedes EI, Pasterkamp G. Intravascular ultrasound elastography in human arteries: initial experience in vitro. *Ultrasound Med Biol.* 1998; 24:401–408. [PubMed: 9587995]
- Dempsey RJ, Vemuganti R, Varghese T, Hermann BP. A review of carotid atherosclerosis and vascular cognitive decline: a new understanding of the keys to symptomology. *Neurosurgery.* 2010; 67:484–493. discussion 93–4. [PubMed: 20644437]
- DePaola N, Gimbrone MA Jr. Davies PF, Dewey CF Jr. Vascular endothelium responds to fluid shear stress gradients. *Arterioscler Thromb.* 1992; 12:1254–1257. [PubMed: 1420084]

- Duff K, Patton D, Schoenberg MR, Mold J, Scott JG, Adams RL. Age- and education-corrected independent normative data for the RBANS in a community dwelling elderly sample. *Clin Neuropsychol*. 2003; 17:351–366. [PubMed: 14704885]
- Elias MF, Sullivan LM, D'Agostino RB, Elias PK, Beiser A, Au R, Seshadri S, DeCarli C, Wolf PA. Framingham stroke risk profile and lowered cognitive performance. *Stroke*. 2004; 35:404–409. [PubMed: 14726556]
- Gao H, Long Q. Effects of varied lipid core volume and fibrous cap thickness on stress distribution in carotid arterial plaques. *J Biomech*. 2008; 41:3053–3059. [PubMed: 18786671]
- Hachinski V, Iadecola C, Petersen RC, Breteler MM, Nyenhuis DL, Black SE, Powers WJ, DeCarli C, Merino JG, Kalaria RN, Vinters HV, Holtzman DM, Rosenberg GA, Wallin A, Dichgans M, Marler JR, Leblanc GG. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. *Stroke*. 2006; 37:2220–2241. [PubMed: 16917086]
- Hansen HH, Lopata RG, de Korte CL. Noninvasive carotid strain imaging using angular compounding at large beam steered angles: validation in vessel phantoms. *IEEE Trans Med Imaging*. 2009; 28:872–880. [PubMed: 19131297]
- Hansen HH, Lopata RG, Idzenga T, de Korte CL. An angular compounding technique using displacement projection for noninvasive ultrasound strain imaging of vessel cross-sections. *Ultrasound Med Biol*. 2010; 36:1947–1956. [PubMed: 20850217]
- Idzenga T, Holewijn S, Hansen HH, de Korte CL. Estimating cyclic shear strain in the common carotid artery using radiofrequency ultrasound. *Ultrasound Med Biol*. 2012; 38:2229–2237. [PubMed: 23062371]
- Kefayati S, Poepping TL. Transitional flow analysis in the carotid artery bifurcation by proper orthogonal decomposition and particle image velocimetry. *Med Eng Phys*. 2013; 35:898–909. [PubMed: 23025907]
- Lee DJ, Sigel B, Swami VK, Justin JR, Gahtan V, O'Brien SP, Dwyer-Joyce L, Feleppa EJ, Roberts AB, Berkowitz HD. Determination of carotid plaque risk by ultrasonic tissue characterization. *Ultrasound Med Biol*. 1998; 24:1291–1299. [PubMed: 10385951]
- Lee RT. Atherosclerotic lesion mechanics versus biology. *Z Kardiol*. 2000; 89(Suppl 2):80–84. [PubMed: 10769408]
- Loree HM, Kamm RD, Atkinson CM, Lee RT. Turbulent pressure fluctuations on surface of model vascular stenoses. *Am J Physiol*. 1991; 261:H644–H650. [PubMed: 1887914]
- Maurice RL, Daronat M, Ohayon J, Stoyanova E, Foster FS, Cloutier G. Non-invasive high-frequency vascular ultrasound elastography. *Phys Med Biol*. 2005; 50:1611–1628. [PubMed: 15798347]
- Maurice RL, Ohayon J, Fretigny Y, Bertrand M, Soulez G, Cloutier G. Noninvasive vascular elastography: theoretical framework. *IEEE Trans Med Imaging*. 2004; 23:164–180. [PubMed: 14964562]
- Maurice RL, Soulez G, Giroux MF, Cloutier G. Noninvasive vascular elastography for carotid artery characterization on subjects without previous history of atherosclerosis. *Med Phys*. 2008; 35:3436–3443. [PubMed: 18777903]
- McCormick M, Rubert N, Varghese T. Bayesian regularization applied to ultrasound strain imaging. *IEEE Trans Biomed Eng*. 2011; 58:1612–1620. [PubMed: 21245002]
- McCormick M, Varghese T, Wang X, Mitchell C, Kliewer MA, Dempsey RJ. Methods for robust in vivo strain estimation in the carotid artery. *Phys Med Biol*. 2012; 57:7329–7353. [PubMed: 23079725]
- Nair A, Calvetti D, Vince DG. Regularized autoregressive analysis of intravascular ultrasound backscatter: improvement in spatial accuracy of tissue maps. *IEEE Trans Ultrason Ferroelectr Freq Control*. 2004; 51:420–431. [PubMed: 15139543]
- Nair A, Kuban BD, Obuchowski N, Vince DG. Assessing spectral algorithms to predict atherosclerotic plaque composition with normalized and raw intravascular ultrasound data. *Ultrasound Med Biol*. 2001; 27:1319–1331. [PubMed: 11731045]
- Nair A, Kuban BD, Tuzcu EM, Schoenhagen P, Nissen SE, Vince DG. Coronary plaque classification with intravascular ultrasound radiofrequency data analysis. *Circulation*. 2002; 106:2200–2206. [PubMed: 12390948]

- Noritomi T, Sigel B, Gahtan V, Swami V, Justin J, Feleppa E, Shirouzu K. In vivo detection of carotid plaque thrombus by ultrasonic tissue characterization. *J Ultrasound Med*. 1997a; 16:107–111. [PubMed: 9166802]
- Noritomi T, Sigel B, Swami V, Justin J, Gahtan V, Chen X, Feleppa EJ, Roberts AB, Shirouzu K. Carotid plaque typing by multiple-parameter ultrasonic tissue characterization. *Ultrasound Med Biol*. 1997b; 23:643–650. [PubMed: 9253812]
- Ophir J, Cespedes I, Ponnekanti H, Yazdi Y, Li X. Elastography: a quantitative method for imaging the elasticity of biological tissues. *Ultrason Imaging*. 1991; 13:111–134. [PubMed: 1858217]
- Picano E, Landini L, Distanto A, Benassi A, Sarnelli R, L'Abbate A. Fibrosis, lipids and calcium in human atherosclerotic plaque. In vitro differentiation from normal aortic walls by ultrasonic attenuation. *Circ Res*. 1985; 56:556–562. [PubMed: 3884177]
- Poepping TL, Rankin RN, Holdsworth DW. Flow patterns in carotid bifurcation models using pulsed Doppler ultrasound: effect of concentric vs. eccentric stenosis on turbulence and recirculation. *Ultrasound Med Biol*. 2010; 36:1125–1134. [PubMed: 20447759]
- Purandare N, Voshaar RC, Hardacre J, Byrne J, McCollum C, Burns A. Cerebral emboli and depressive symptoms in dementia. *Br J Psychiatry*. 2006; 189:260–263. [PubMed: 16946362]
- Purandare N, Voshaar RC, Morris J, Byrne JE, Wren J, Heller RF, McCollum CN, Burns A. Asymptomatic spontaneous cerebral emboli predict cognitive and functional decline in dementia. *Biol Psychiatry*. 2007; 62:339–344. [PubMed: 17531959]
- Randolph C, Tierney MC, Mohr E, Chase TN. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. *J Clin Exp Neuropsychol*. 1998; 20:310–319. [PubMed: 9845158]
- Reininger AJ, Reininger CB, Heinzmann U, Wurzing LJ. Residence time in niches of stagnant flow determines fibrin clot formation in an arterial branching model—detailed flow analysis and experimental results. *Thromb Haemost*. 1995; 74:916–922. [PubMed: 8571321]
- Ribbers H, Lopata RG, Holeyijn S, Pasterkamp G, Blankensteijn JD, de Korte CL. Noninvasive two-dimensional strain imaging of arteries: validation in phantoms and preliminary experience in carotid arteries in vivo. *Ultrasound Med Biol*. 2007; 33:530–540. [PubMed: 17280769]
- Richardson PD, Davies MJ, Born GV. Influence of plaque configuration and stress distribution on fissuring of coronary atherosclerotic plaques. *Lancet*. 1989; 2:941–944. [PubMed: 2571862]
- Rocque BG, Jackson D, Varghese T, Hermann B, McCormick M, Kliewer M, Mitchell C, Dempsey RJ. Impaired cognitive function in patients with atherosclerotic carotid stenosis and correlation with ultrasound strain measurements. *J Neurol Sci*. 2012; 322:20–24. [PubMed: 22658531]
- Roth SL, Hastings HM, Evans SJ, Esposito M, Gladstone C, Rathod S, Bodenheimer MM. Spectral analysis of demodulated ultrasound returns: detection of scatterer periodicity and application to tissue classification. *Ultrason Imaging*. 1997; 19:266–277. [PubMed: 9651954]
- Schaar JA, De Korte CL, Mastik F, Strijder C, Pasterkamp G, Boersma E, Serruys PW, Van Der Steen AF. Characterizing vulnerable plaque features with intravascular elastography. *Circulation*. 2003; 108:2636–2641. [PubMed: 14581406]
- Schmitt C, Soulez G, Maurice RL, Giroux MF, Cloutier G. Noninvasive vascular elastography: toward a complementary characterization tool of atherosclerosis in carotid arteries. *Ultrasound Med Biol*. 2007; 33:1841–1858. [PubMed: 17698283]
- Shi H, Mitchell CC, McCormick M, Kliewer MA, Dempsey RJ, Varghese T. Preliminary in vivo atherosclerotic carotid plaque characterization using the accumulated axial strain and relative lateral shift strain indices. *Phys Med Biol*. 2008a; 53:6377–6394. [PubMed: 18941278]
- Shi H, Varghese T. Two-dimensional multi-level strain estimation for discontinuous tissue. *Phys Med Biol*. 2007; 52:389–401. [PubMed: 17202622]
- Shi H, Varghese T, Dempsey RJ, Salamat MS, Zagzebski JA. Relationship between ultrasonic attenuation, size and axial strain parameters for ex vivo atherosclerotic carotid plaque. *Ultrasound Med Biol*. 2008b; 34:1666–1677. [PubMed: 18490099]
- Shi H, Varghese T, Mitchell CC, McCormick M, Dempsey RJ, Kliewer MA. In vivo attenuation and equivalent scatterer size parameters for atherosclerotic carotid plaque: preliminary results. *Ultrasonics*. 2009; 49:779–785. [PubMed: 19640556]

- Slager CJ, Wentzel JJ, Gijzen FJ, Schuurbiers JC, van der Wal AC, van der Steen AF, Serruys PW. The role of shear stress in the generation of rupture-prone vulnerable plaques. *Nat Clin Pract Cardiovasc Med*. 2005; 2:401–407. [PubMed: 16119702]
- Stein PD, Sabbah HN. Measured turbulence and its effect on thrombus formation. *Circ Res*. 1974; 35:608–614. [PubMed: 4278187]
- van der Wal AC, Becker AE. Atherosclerotic plaque rupture--pathologic basis of plaque stability and instability. *Cardiovasc Res*. 1999; 41:334–344. [PubMed: 10341833]
- Varghese T. Quasi-Static Ultrasound Elastography. *Ultrasound Clin*. 2009; 4:323–338. [PubMed: 20798841]
- Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med*. 2003; 348:1215–1222. [PubMed: 12660385]
- Whisnant JP, Basford JR, Bernstein EF, Cooper ES, Dyken ML, Easton JD, Little JR, Marler JR, Millikan CH, Petito CK, Price TR, Raichle ME, Robertson JT, Thiele B, Walker MD, Zimmerman aRA. Special report from the National Institute of Neurological Disorders and Stroke. Classification of cerebrovascular diseases III. *Stroke*. 1990; 21:637–676. [PubMed: 2326846]
- Wilson LS, Neale ML, Talhami HE, Appleberg M. Preliminary results from attenuation-slope mapping of plaque using intravascular ultrasound. *Ultrasound Med Biol*. 1994; 20:529–542. [PubMed: 7998374]

(a)

(b)

Figure 1.
B-mode image (a) and segmented plaque on B-mode image (b).

(a)

(b)

(c)

Figure 2. Axial strain values overlaid on the B-mode image (a). Mean values in the small ROI and entire plaque are shown in (b), and their standard deviations in (c).

(a)

(b)

(c)

Figure 3. Lateral strain values overlaid on the B-mode image (a). Mean values in the small ROI and entire plaque are shown in (b), and their standard deviations in (c).

(a)

(b)

(c)

Figure 4. Shear strain values overlaid on the B-mode image (a). Mean values in the small ROI and entire plaque are shown in (b), and their standard deviations in (c).

Figure 5.

Legend for all the remaining plots of the RBANS Total score versus strain indices. The Circle denotes symptomatic patients, cross denotes asymptomatic patients, and square denotes questionable patients. The dotted line represents the linear fit for symptomatic patients, dashed line for asymptomatic patients, and solid line for all patients.

(a)

(b)

(c)

Figure 6. Linear least square fits of RBANS Total score with maximum (a), absolute minimum (b), and peak-to-peak (c) axial strain averaged over the small ROI.

(a)

(b)

(c)

Figure 7. Linear least square fits of RBANS Total score with maximum (a), absolute minimum (b), and peak-to-peak (c) lateral strain averaged over the small ROI.

(a)

(b)

(c)

Figure 8. Linear least square fits of RBANS Total score with maximum (a), absolute minimum (b), and peak-to-peak (c) shear strain averaged over the small ROI.

(a)

(b)

(c)

Figure 9.

Linear least square fits of RBANS Total score with the maximum axial (a), lateral (b) and shear (c) strain averaged over the entire plaque.

(a)

(b)

(c)

Figure 10.

Linear least square fit of the RBANS Total score with peak-to-peak axial (a), lateral (b) and shear (c) strain averaged over the entire plaque.

Table 1

Human subject information for this study.

Clinical Classification	Subject Number	Sex	Age	BMI	Plaque Dimension (mm ²)	Total RBANS Score	Maximum Axial Strain	Maximum Lateral Strain	Maximum Shear Strain
Symptomatic	1	F	79	18.1	36.67	82	16	13.59	16.45
	2	M	72	28.5	28.95	63	28	20.90	34.96
	3	M	72	36.5	148.62	72	26	15.72	21.58
	4	F	72	28	28.81	68	11.2	12.92	32.22
	5	M	71	29	39.29	72	15.6	22.19	13.97
	6	M	57	29.5	72.26	72	3.6	2.44	3.31
	7	M	66	27.3	78.86	83	30	14.68	13.88
	8	M	68	35	28.65	91	14.7	7.05	4.96
	9	M	63	27.3	25.34	88	18.6	14.09	32.46
	10	M	44	35.1	75.63	100	12.88	5.15	25.79
	11	M	62	29.6	14.59	116	4.45	3.09	8.41
	12	M	75	27.3	46.59	121	5.58	7.23	9.52
	13	M	75	30.8	120.97	100	7.21	4.84	13.02
	14	M	61	27.2	49.68	88	25.85	4.73	11.20
	15	M	49	28.3	100.85	78	20.68	16.54	30.11
	16	M	59	25.1	31.25	95	7.2	4.48	18.56
	Mean $\pm$ Standard Deviation		65.31 $\pm$ 9.71	28.91 $\pm$ 4.33	57.94 $\pm$ 38.46	86.81 $\pm$ 16.63	15.47 $\pm$ 8.74	10.60 $\pm$ 6.46	18.15 $\pm$ 10.25
Asymptomatic	17	F	61	35.9	24.59	78	45	19.40	27.24
	18	F	74	27.1	27.95	86	11.3	9.76	15.21
	19	F	71	29.3	35.53	71	18.4	5.12	8.68
	20	F	59	N/A	33.85	85	19.83	7.99	16.39
	21	F	60	25.3	45.08	92	10.88	10.65	21.36
	22	M	63	26.9	83.32	81	23.11	25.20	34.26
	23	F	75	30.4	35.64	91	12.48	8.50	13.89

Clinical Classification	Subject Number	Sex	Age	BMI	Plaque Dimension (mm ²)	Total RBANS Score	Maximum Axial Strain	Maximum Lateral Strain	Maximum Shear Strain
	Mean $\pm$ Standard Deviation		66.14 $\pm$ 6.94	29.15 $\pm$ 3.77	40.85 $\pm$ 19.82	83.43 $\pm$ 7.41	20.14 $\pm$ 11.92	12.38 $\pm$ 7.19	19.58 $\pm$ 8.73
Questionable	24	M	73	32.8	29.76	89	17	20.25	29.43
All patients	Mean $\pm$ Standard Deviation		65.88 $\pm$ 8.74	29.14 $\pm$ 4.08	51.78 $\pm$ 33.93	85.92 $\pm$ 14.06	16.90 $\pm$ 9.57	11.52 $\pm$ 6.70	19.04 $\pm$ 9.68