Carotid atherosclerotic plaque instability and cognition determined by ultrasound-measured plaque strain in asymptomatic patients with significant stenosis

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OBJECTIVE This article describes the use of ultrasound measurements of physical strain within carotid atherosclerotic plaques as a measure of instability and the potential for vascular cognitive decline, microemboli, and white matter changes.

METHODS Asymptomatic patients with significant (> 60%) carotid artery stenosis were studied for dynamic measures of plaque instability, presence of microemboli, white matter changes, and vascular cognitive decline in comparison with normative controls and premorbid state.

RESULTS Although classically asymptomatic, these patients showed vascular cognitive decline. The degree of strain instability measured within the atherosclerotic plaque directly predicted vascular cognitive decline in these patients thought previously to be asymptomatic according to classic criteria. Furthermore, 26% of patients showed microemboli, and patients had twice as much white matter hyperintensity as controls.

CONCLUSIONS These data show that physical measures of plaque instability are possible through interpretation of ultrasound strain data during pulsation, which may be more clinically relevant than solely measuring degree of stenosis. The data also highlight the importance of understanding that the definition of symptoms should not be limited to motor, speech, and vision function but underscore the role of vascular cognitive decline in the pathophysiology of carotid atherosclerotic disease.

Clinical trial registration no.: NCT02476396 (clinicaltrials.gov)

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KEY WORDS carotid atherosclerosis; ultrasound; vascular cognitive decline; plaque instability; ultrasound strain; stroke; vascular disorders

Sᴛʀᴏᴋᴇ remains a significant cause of disability worldwide, and considerable efforts are ongoing to prevent cerebrovascular events. Historically, ischemic stroke prevention has included reducing cardiac emboli; intensive medical therapy addressing coagulation, rheology, blood pressure, atherosclerosis-related risk factors; and surgery (carotid endarterectomy and carotid artery [CA] stent-ing). Continued advancements on all fronts have raised the question of the need for improvements in the diagnosis of the at-risk patient population. This is especially important in patients who present asymptomatically with atherosclerotic disease. Unlike the case of severe symptomatic CA stenosis (CAS), the benefit of surgical intervention in asymptomatic CAS is less pronounced.[1] Studies have sug-

gested that the strategy of operating upon patients with asymptomatic, > 60% stenosis would require an estimated 40 carotid endarterectomies to prevent one stroke in 5 years.[26] Multiple studies have suggested that such aggressive treatment requires improved methods to identify patients with unstable plaques who are truly at risk.[6,9,13,14,17,26] If the degree of stenosis in asymptomatic patients does not well predict CA plaque thromboembolism, then surgery guided by severity of luminal stenosis alone is an unsustainable strategy into the future because of both cost and a poor risk-benefit ratio.[22,27]

A scientific approach to this clinical question would be the measurement of the physical instability of CA plaques during pulsation. Such a measure would allow a biomechanical analysis of the propensity for a plaque to fracture during pulsation, which could result in creating an embolic or thromboembolic event. That biomechanical analysis must take into account the morphology of the plaque, the peak stress within the cap of the plaque, and its ability to create emboli and/or other clinically recognizable deficits.

Carotid Artery Plaque Instability and Cognitive Symptoms

The consequences of unrecognized emboli or silent strokes may be quite profound. Recent imaging studies suggest a far larger number of ischemic events are taking place than are recognized by our present clinical examinations.[19] Estimates are up to 11 million/year of so-called "silent strokes" in patients at risk.[31,32] Silent stroke and vascular cognitive decline may not be easily detected by standard clinical exam examination, but silent stroke may occur with concurrent subclinical emboli.[8,17,337,38,39,40,41] Microemboli may cause cognitive impairment through rupture of vulnerable plaques,[28,37–39] either through rupture of the thin fibrous cap or through hemorrhage and thrombosis.[37,38] Our studies of high-grade stenosis including patients having prior stroke or transient ischemic attack (TIA) suggest that vascular cognitive decline is seen in these patients and is directly related to the degree of physical instability of carotid atherosclerotic plaque.[37]

Measures of Plaque Instability

A parameter of physical stability of the CA plaque may be far more important than its degree of stenosis in predicting patients at risk and has been a target of research regarding measures of plaque vulnerability. Recent studies[12] have suggested the histopathological classification of such plaques to be of importance postoperatively but have not found a good MRI criteria for preoperative assessment of plaque stability. In the 1980s and 1990s imaging methods emphasized imaging lumen over vessel wall. Therefore, the available imaging studies primarily looked at the residual lumen as a surrogate for significance of plaque. With modern MRI and ultrasound imaging we can now look at the plaque and vessel wall in a more sophisticated fashion in an attempt to determine its physical instability or strain during pulsation.[30] Deformation of the plaque with pulsation has been associated with cognitive decline through embolization.[8,25,38,39] The shear strain elasticity index has been used as a potential assessment of vulnerability within the plaque.[18,37] Such studies have been correlated with high-

resolution brain MR spectroscopy and MRI.[4,37] We have previously shown in patients that include those with strokes that this measure of strain in significant plaques correlates with MRI measures of brain white matter hyperintensities (WMHs).[4] This suggests that carotid atherosclerotic instability may not only be a marker of advanced plaque formation and potential emboli from that site, but may also be a marker of the systemic degree of atherosclerotic disease affecting both large and small vessels. Therefore, a CA bifurcation deposit of atherosclerosis, which is accessible to noninvasive measurement, may also act as a marker for patients at risk for total symptomatology and may measure its individual stability. In this article, we describe the utility of noninvasive ultrasound measurements of physical strain within the pulsating atherosclerotic plaque as a potential biomarker to determine which asymptomatic patients are at greatest risk for future symptomatology of all types, especially vascular cognitive decline. Previous work has looked at patients unspecified for previous symptomatology and has shown a significant correlation between increase in CA strain and decrease in cognitive function.[16,26] Such a correlation was not seen for the degree of stenosis. We wished to analyze whether such criteria are present in asymptomatic patients, suggesting a potential utility of this method for the early identification of patients at greatest risk for eventual plaque rupture or systemic symptomatology. If such criteria can distinguish vulnerable from stable plaques through biomechanical stress analysis, we would be able to direct treatment, be it medical or surgical, to the patients at greatest risk and spare patients with asymptomatic but stable stenosis from unnecessary treatment.

Methods
Participants

Twenty-seven asymptomatic patients with significant (> 60%) CA plaque in the University of Wisconsin Atherosclerotic Plaque Study were evaluated for medical comorbidities, cognition, and an ultrasound-based biomechanical determination of strain within the plaque during pulsation. A subset of the group was studied for the presence of cerebral emboli, as well as MRI evidence of cerebral microvascular brain changes. All preoperative testing was performed in accordance with the Health Sciences IRB of the University of Wisconsin–Madison. All patients provided written informed consent. This study is part of a trial (clinical trial registration no.: NCT02476396 [clinicaltrials.gov]).

Each patient was assessed by a faculty member of the University of Wisconsin Comprehensive Stroke Center to determine asymptomatic status relative to the CA in question. All patients met the following inclusion criteria: age 18 years or older, native English speaking, and asymptomatic CAS as measured by the Asymptomatic Carotid Atherosclerotic Trial criteria. Patients were excluded if they had known dementia or an inability to cooperate in the study; history of TIA or stroke; history of CA procedures or cervical radiotherapy; or other medical conditions that would interfere with the ability to cooperate with testing. Cognitive assessments and ultrasound images were conducted separately in a blinded fashion.

Neuropsychological Assessment

Each participant was administered the 60-minute neuropsychological test protocol recommended by the National Institute of Neurological Disorders and Canadian Stroke Network. This protocol was selected specifically for stroke patients and assesses several important functional domains with tests of executive function/attention, speeded psychomotor, verbal and nonverbal memory, language, and visuospatial skills. For the current study, widely used verbal and performance IQ measures (Wechsler Adult Intelligence Scale–IV, Digit Span, and Block Design) were added.

All test scores were corrected for age and sex, published norms, or covariate analysis. Scores on semantic and category fluency tasks, in addition to Trails A and B (Trail making Test), were converted to standardized scores using the Revised Comprehensive Norms for an Expanded Halstead-Reitan Battery. Results of other tests were age-normed using materials provided with each test.

Plaque Stability as Measured by Ultrasound Strain

Ultrasound Data Acquisition for Carotid Strain Imaging

Noninvasive clinical and research ultrasound acquisitions were performed on patients after obtaining informed consent, under a protocol approved by the University of Wisconsin–Madison IRB. A standard ultrasound clinical examination was performed on each patient and followed by acquisition of research data. Typically, each CA was scanned with ultrasound as were the common CA, internal ICA and CA bulb, taking care to keep the vessel walls parallel to the 2D imaging plane and the transducer.

Ultrasound radiofrequency echo signals were acquired and stored for offline processing over several cardiac cycles along with clinical B-mode images and color flow Doppler images, using a Siemens S2000 Ultrasound system equipped with a 18L6 linear array transducer. A transmit center frequency of 11.4 MHz, with a single transmit focus set at the depth of the plaque and a sampling frequency of 40 MHz, was used for F data acquisition.

Plaque regions with adventitia were segmented using the Medical Imaging Interaction Toolkit by a research sonographer on the end diastolic frame in B-mode images reconstructed from radiofrequency data. The segmentation was then transferred to the entire loop of radiofrequency data. Images were reviewed over the entire cardiac cycle to allow point-by-point comparison of vessel wall to plaque borders. A hierarchical block-matching motion tracking algorithm[20] was used, by tracking the deformation over the segmented plaque region from the diastolic to systolic frame over 2 cardiac cycles.[37] A dynamic frame skip methodology, with smaller frame skips during systole and larger frame skips during diastole for efficient strain estimation, was incorporated. Local displacements were tracked using 2D normalized cross-correlation analysis with recursive Bayesian regularization[20] over 3 iterations and finally were filtered with a 3 × 3–pixel (0.06 mm × 0.225–mm) median filter to eliminate any peak hopping artifacts. Local subsample displacements[20] were accumulated over a cardiac cycle to determine the cumulative displacement and strain variations over a cardiac cycle. Local strain tensors were computed using a modified least-squares fit over a 7-pixel linear segment. The accumulated maximum axial, lateral, and shear strain indices over a cardiac cycle were computed for each patient and used for the correlation with cognitive variables.[39,40]

Transcranial Doppler Detection of Emboli

Transcranial Doppler (TCD) examination was performed with the SONORA Digital Bilateral Systems (Natus) using a 2.0-MHz transducer to image both middle cerebral arteries (MCAs) through the transtemporal window. Monitoring lasted for an hour, and the total number of high-intensity transient signals (HITSs) was recorded. Images were reviewed after each session by a physician and 2 observers.

The TCD system used an embolus detection algorithm to identify HITSs in the MCA suggestive of microemboli. The criteria used to distinguish HITSs from artifacts were: 1) high-intensity signal compared with the background blood flow, signal detected by system, 2) unidirectional signal within the Doppler velocity spectrum, 3) transient signal less than 300 msec in duration, 4) the presence of an audible noise (moan, chirp, click, thud) (Consensus Committee of the Ninth International Cerebral Hemodynamic Symposium, 1995), and 5) a change in complex mode. Two observers and a physician reviewed all HITSs to distinguish those suggestive of microemboli from artifacts. The TCD examination was considered positive for the presence of microemboli if one or more HITSs were detected during the 60-minute monitoring period.

MRI WMHs

MRI measures of brain white matter changes or white matter hyperintensities seen on T2 flair MRI signals are postulated to result from cumulative microvascular injury. We chose this feature as a measure of the target organ for both microvascular changes and subclinical embolus disease in these clinically asymptomatic patients.

A subset of participants who were free from MRI contraindications (nonremovable metal implants, pregnancy, inability to lie still for approximately 1 hour) were scanned on a 3-T GE ×750 MRI scanner. The scan sequences acquired relevant to the present paper include T1-weighted and T2-weighted FLAIR scans. The T1-weighted scan parameters were as follows: acquired in the axial plane with a 3D fast–spoiled gradient echo sequence; TI 450 msec; TR 8.1 ms; TE 3.2 msec; flip angle 12°; acquisition matrix 256 × 256 mm; FOV 256 mm; and slice thickness 1.0 mm. T2-weighted FLAIR scan parameters were as follows: acquired in the sagittal plane; TI 1868 msec; TR 6000 msec; TE 123 msec; flip angle 90°; acquisition matrix 256 × 256 mm; FOV 256 mm; slice thickness 2.0 mm; and no gap yielding, a voxel resolution of 1 × 1 × 2 mm.[4]

As this project has a significant vascular focus, we decided to focus on WMHs, a metric believed to represent cumulative vascular injury to the brain. To determine the extent/volume of WMHs, Statistical Parametric Mapping Software (SPM8) with the Lesion Segmentation Tool extension developed by Schmidt in 2012 was used. The Lesion Segmentation Tool allows for computerized, as opposed to manual, tracing of the WMH lesions. This
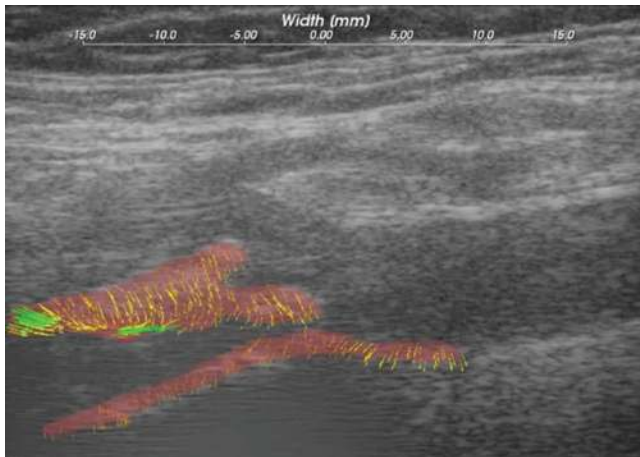
FIG. 1. B-mode reconstructed from RF data segmented plaque with adventitia, showing displacement vectors (direction of local deformation) with cardiac pulsation.

eliminates issues of interrater reliability and subjectivity. In validating the method, the developer applied it to a cohort of multiple sclerosis patients and found an extremely high correlation with hand-tracing, which is evidence of the validity of this method ($R^2 = 0.94$).[29] We compared the subjects in the present study to previously acquired data obtained in age-matched, cognitively healthy participants from the Wisconsin Alzheimer's Disease Research Center. These 64 controls had the following demographics: mean age 69 years, 57.8% female, 45.3% on blood pressure medication, 15.6% had diabetes, and a mean total cholesterol of 190.

Results

We studied 27 asymptomatic patients with > 60% CAS in the current analysis. The patients had an average age of 71.0 years (SD 7.22, range 57–84 years), 13 were female, and 14 were male. Comorbid risk factors included the presence of known heart disease in 12 (52%), lipid abnormalities in 22 (82%), diabetes in 7 (26%), previous or current smoking (yes/no) in 18 (67.4%), and hypertension in 23 (85%). Eighty-nine percent were taking aspirin and 70% were being treated for lipid abnormalities.

Ultrasound strain yielded a dynamic picture of the presence and degree of instability during pulsation. Figure 1 shows the force lines of strain developing in a pulsating plaque at the origin of the internal CA. These in turn are quantified using the maximal axial, lateral, and shear strain. Figure 2 shows findings from a patient with higher strain and high plaque stenosis, and Fig. 3 shows findings from a patient with lower strain and less plaque stenosis.

The relationship between baseline cognition and strain was assessed using zero order and partial correlations. Significance was assessed at $p < 0.05$. At least one maximum strain variable (lateral, axial, or shear) predicted cognitive scores on 4 of 14 tests. Multiple strain measures shared overlapping variance predictive of cognition; the best predictor from the 3 strain variables is given after each variable, along with the correlation coefficient. As described above, all analyses controlled for age and sex (see Table 1).

Poor performance on tasks of simple motor ability (Trails A; $r = -0.47$, $p = 0.01$) and complex motor/executive function ($r = -0.564$, $p = 0.002$) was associated with increased maximum lateral strain. Low scores on another test of complex motor ability and executive function (Digit Symbol) were associated with increased maximum shear strain ($r = 0.84$, $p < 0.001$), as were visual-motor construction deficits (Block Design; $r = -0.47$, $p = 0.019$).

Nearly all relationships were negative: high strain was associated with poor cognition (see Fig. 4).

High axial strain in carotid atherosclerotic plaque as measured by ultrasound during pulsation was associated with decreased cognitive performance on tests of language, motor function, working memory, visual-motor construction, and executive function. This is true even in the absence of overt symptoms of TIA or stroke.

When evaluating the spectrum of vascular cognitive decline versus the maximum strain value within the plaque with pulsation, we observed age-corrected negative correlations between maximum strain value and the following cognitive abilities: motor sequencing, executive
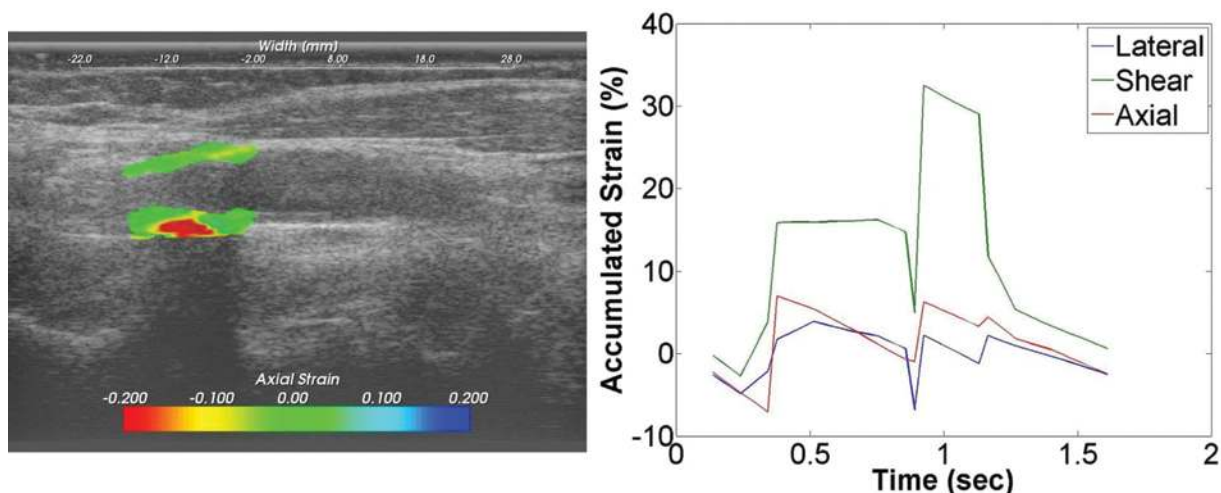
FIG. 2. **Left:** Strain images superimposed on ultrasound B-mode images obtained in an asymptomatic patient with higher values of the accumulated strain. **Right:** Plot of the accumulated strain over 2 cardiac cycles.
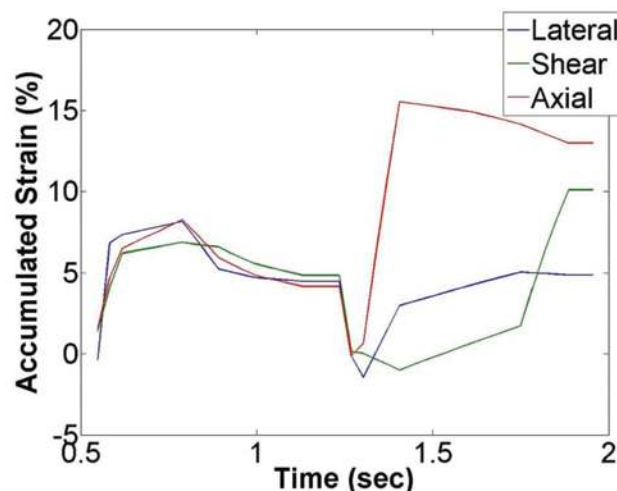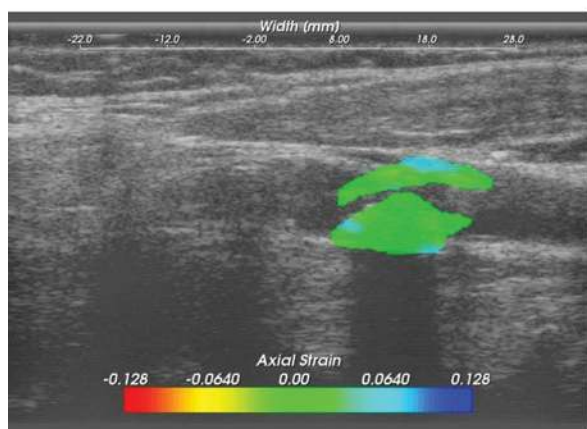
FIG. 3. **Left:** Strain images superimposed on ultrasound B-mode images obtained in an asymptomatic patient with lower values of the accumulated strain. **Right:** Plot of the accumulated strain over 2 cardiac cycles.

function, and visual-motor reproduction, as well as general knowledge, as illustrated in Table 1. Several of the cognition variables had significant p values < 0.01 as shown in Table 1. Each of the 3 measures of the maximum strain predicted cognitive variables at p < 0.05. Worse cognition was always associated with increased strain indices. For most variables, all 3 maximum strain variables predicted cognitive decrement. All analyses controlled for age and sex. It is important to note that in classically asymptomatic patient the loss of cognition was seen in executive cognitive function (cognitive assessment tools: Trails A and Trails B from the Trail Making Test, and the Digit Symbol and Block Design tests) before marked changes were seen in memory parameters.

White Matter Hyperintensities and TCD Emboli Detection

We saw mean WMH changes of 54.6 ml in 13 patients studied with MRI. In our age-matched control population (n = 64), WMH was a mean of 25.3 ml (p = 0.006) (Fig. 5). Although in this small sample size, increasing white matter changes trended with but did not correlate with increasing strain, it is possible that would be the case in a larger sample size. The degree of WMH changes was considered surprising given the classically asymptomatic nature of this population.

Similarly, in a period of only 1 hour of testing, 6 (26%) of 23 classically asymptomatic patients tested demonstrated HITSs in the MCA, showing microemboli, and 9% had contralateral emboli. Although the degree of plaque strain trended with but could not significantly predict the presence or absence of emboli in this small sample group (p = 0.15), this percentage of patients with emboli dramatically differs from what has been reported for healthy control patients[7,34] (zero) (p = 0.005) and is considered to be consistent with one etiology of vascular cognitive decline—subclinical emboli. Tong et al., Deklunder et al., and others have showed an expected zero rate of emboli in controls.[5,7,11,15,23,24,33,34] The emboli detected in our study (Fig. 6) were seen during only 1 hour of testing. It is unknown what data might have resulted from longer periods of testing. HITSs suggestive of microemboli were present

in 26% of our asymptomatic patients, within the 1-hour TCD monitoring period, suggesting that while the patients did not present with classic TIA or stroke, their plaques may not have been stable and that microemboli from vulnerable plaque may be contributing to cognitive decline.

TABLE 1. Summary of strain values

Variable	Correlation Coefficient (p value)		
	Max Axial Strain	Max Lat Strain	Max Shear Strain
Category Fluency	−0.278 (0.161)	−0.355 (0.069)	−0.215 (0.281)
Letter Fluency	0.035 (0.861)	−0.039 (0.849)	0.028 (0.891)
Confrontation Naming	−0.242 (0.245)	−0.213 (0.306)	−0.121 (0.564)
Trails A	−0.412 (0.033)*	**−0.468 (0.014)***	−0.398 (0.040)*
Trails B	−0.475 (0.012)*	**−0.563 (0.002)***	−0.516 (0.006)*
Digit Symbol	−0.806 (<0.001)*	−0.721 (<0.001)*	**−0.839 (<0.001)***
Block Design	−0.433 (0.031)	−0.236 (0.256)	**−0.465 (0.019)***
Information	−0.359 (0.078)	−0.048 (0.820)	−0.250(0.228)
Digit Span	−0.194 (0.352)	−0.192 (0.359)	−0.087 (0.681)
Verbal Memory— Immediate	−0.294 (0.145)	−0.156 (0.447)	−0.313 (0.120)
Verbal Memory— Delayed	−0.189 (0.355)	0.051 (0.820)	−0.146 (0.476)
Nonverbal Memory— Immediate	−0.246 (0.226)	−0.062 (0.763)	−0.234 (0.250)
Nonverbal Memory— Delayed	−0.251 (0.215)	−0.106 (0.605)	−0.236 (0.245)
Figure Copy	−0.241 (0.246)	−0.195 (0.350)	−0.337 (0.099)

High strain values are associated with low cognition scores.
* Denotes significance at p = 0.05. The strongest significant correlation with strain is in boldface for each cognitive variable.
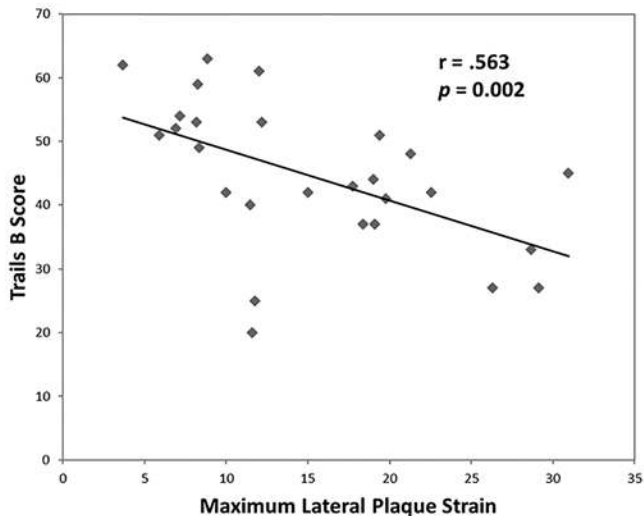
FIG. 4. Decline in Trails B Executive Function correlated with increase in maximal plaque (p = 0.002).

Discussion

Stenosis—Emboli and Symptoms

Carotid artery surgery in response to cerebrovascular symptomatology dates back to the early work of Eastcott and colleages.[10] Over the subsequent decades, the number of interventions, both by endarterectomy and by stenting, have increased. The major landmark study, the North American Carotid Endarterectomy Trial (NASCET), first published in 1992, described a benefit for symptomatic patients with significant CAS who underwent surgery.[2,3] These studies ushered in the use of CAS, defined in various studies as becoming significant at 50%, 60%, or 70% stenosis, as primary criteria for justification of surgery. Subsequent studies[36] suggested that such parameters may be useful in asymptomatic disease and surgical intervention rapidly increased based on this parameter. It is important to understand that carotid atherosclerotic disease is primarily an embolic phenomenon. While the degree of stenosis may

reach a point that would restrict flow, due to the individual characteristics of the circle of Willis, flow characteristics of single-vessel stenosis cannot reliably predict cerebral ischemia. At the same time, CA plaque emboli generally are a size that often localizes beyond the circle of Willis, primarily in vessels with only pial-to-pial collaterals. Such emboli may reliably result in loss of function to a region of brain that may or may not be clinically recognized due to its regional presence or absence of eloquence.

In our previous study,[35] plaque strain was definitely affected by pulsation and instability of the plaques from our earlier stroke paper. We feel that this is related to neovascularity. The question is whether medications may affect this. Theoretically, antiplatelet therapy such as aspirin may decrease emboli but could theoretically increase plaque hemorrhage. Statins may theoretically stabilize plaque or stabilize the cholesterol deposits. In the present study group, 89% were taking aspirin and 70% were being treated for lipid abnormalities. The common use of both medications in patients with atherosclerotic disease may preclude controlled studies of their effect on strain. The data from the present paper neither confirm nor deny either of these potential effects of the medications and indeed make an interesting argument for future studies of medication effects in relation to strain. It is not known if medications such as aspirin or statins affect vessel strain or instability.

A significant concern for loss of function that may not be clinically recognized is that of vascular cognitive decline. While this is of extraordinary importance to the patients, it is not a standard part of the evaluation for determining symptomatic or asymptomatic status. However, imaging studies suggest that several million "silent strokes" may be missed per year in patients at risk,[31,32] and further vascular cognitive decline has been shown to occur with concurrent subclinical emboli.[8,25,39,41] By instituting a standardized examination for vascular cognitive decline, we discovered that it existed in all of our study patients harboring large CA bifurcation plaques in spite of their classically asymptomatic status.
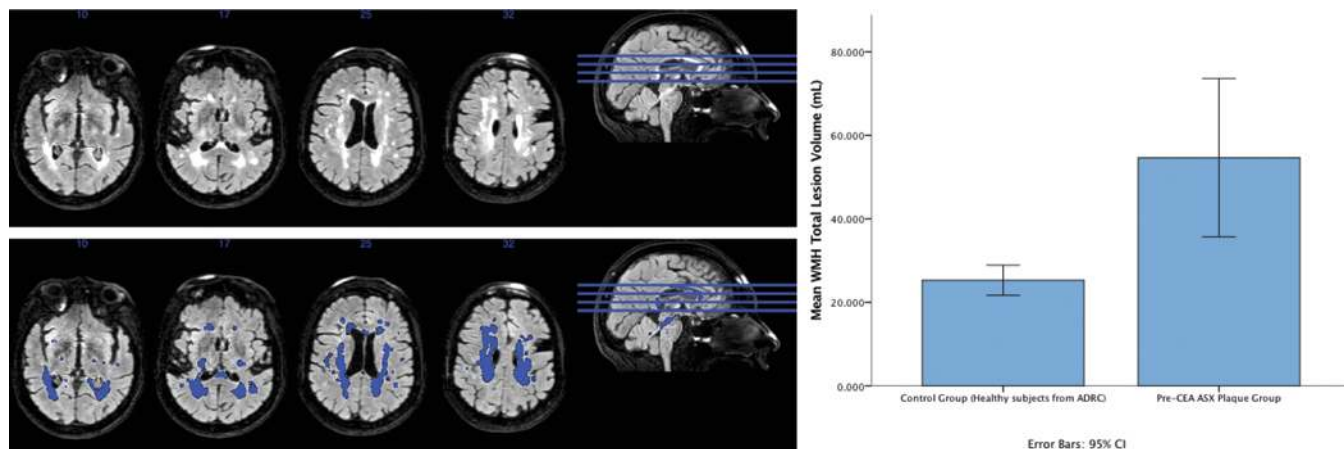

FIG. 5. Images showing WMHs in an asymptomatic patient (**left**) and graph showing WMH lesion volume in 13 patients with asymptomatic plaques (**right**). The mean WMH total lesion volume (TLV) in the 64 control individuals was 25.30639 ml (mean age 69.06 ± 4.52 years), and the mean WMH TLV in the 13 patients with asymptomatic plaques was 54.64323 ml (mean age 69.62 ± 6.79 years) (independent 2-tailed t-test for WMH TLV: p = 0.006). The asymptomatic plaque group had statistically greater WMH TLV than the ADRC control group. ADRC = Alzheimer's Disease Research Center; ASX = asymptomatic.
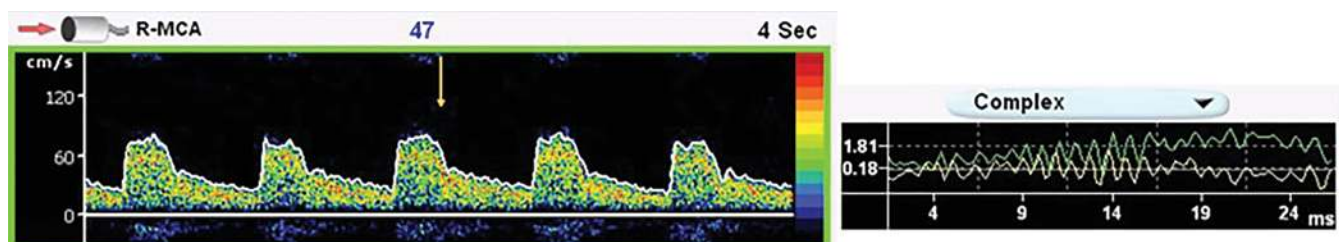
FIG. 6. TCD signal from the right MCA with the HITS identified by the *yellow arrow*. This HITS was also accompanied by an audible chirp, a change in complex, and was less than 300 msec in duration.

Baseline cognitive decline was significant in all patients, but the degree of significance of the cognitive decline at presentation varied. Strain measurement also varied in the asymptomatic patients. However, the degree of strain or instability was directly correlated with the degree of cognitive decline. Our results also suggest that this effect is best represented in loss of executive function before memory is lost.

We estimated both the axial and lateral displacement vectors and corresponding strain tensor components (axial and lateral) within the 2D ultrasound imaging plane. Axial strains refer to the strain estimated along the direction of ultrasound beam propagation, while the lateral strains are estimated perpendicular to this direction, due to blood flow expanding and relaxing the vessel during systole as opposed to diastole. Note that for an intact CA plaque enclosed within a thicker fibrous cap, most of the deformation is anticipated along the axial or beam direction. For softer plaques or those with increased fissuring, increased lateral strains are observed, due to the movement of the plaque in the direction of blood flow during systole. Similar to what is seen in symptomatic patients, increased lateral strains were observed in asymptomatic patients with lower cognitive scores, possibly indicating that microembolization was occurring in these patients, with plaque being deformed along the direction of blood flow (instead of against the artery wall), which may lead to emboli being released into the bloodstream. Identification of this type of plaque deformation may be critical in identifying vulnerable plaque, as the deformation could be due to weakening of the plaque capsule, leading to fatigue failure or rupture even with the normal repeated alternating or cyclic stresses induced due to blood flow. Both the axial and lateral deformations contribute to the increased shearing strains in the artery. Increased shearing strains are an indicator of the presence of increased stress concentrations typically at boundary locations of the plaque with the artery wall, indicating regions at a potentially of high risk for rupture. In general, a higher probability of rupture would exist at locations with these stress concentrations.

The mean axial strain index over a cardiac cycle ranged from 3.9% to 89.16% (mean 32.94% ± 31.92%), while the mean lateral strain index ranged from 3.7% to 30.95% (mean 15.98% ± 8.21%) and the mean shear strain index ranged from 6.64% to 93.36% (mean 36.33% ± 29.65%) in these asymptomatic patients. The significant variability in the mean axial strain index in this group might indicate that many of these patients could soon experience progression to gross symptoms due to fissuring or rupture of their plaque, whereas the others with lower strain indices might

remain asymptomatic due to the lower plaque deformations either due to the plaque being calcified or the presence of a thick fibrous cap. Relationships between other measures of the physics of vessel wall strain and anatomy need further study.

We saw a striking amount of WMH and emboli in these asymptomatic patients. We noted a doubling of the WMH change over controls and 26% of those tested had emboli in only a 1-hour sample. We have previously shown the importance of both WMH and TCD-detected emboli in atherosclerotic patients not selected for symptomatic or asymptomatic status. In that group, we showed significant correlations among measurements of axial, lateral, peak-to-peak, and shear plaque strain, and the total amount of WMH in the brain.[4] In that prior study our subjects had a mean WMH lesion burden of almost 2 standard deviations greater than the normal age-matched population (WMH z-scores range from −0.76 to 5.96 with a mean of 1.81).[4] In that study the presence of HITSs was associated with an increase in the WHM lesion burden—β of 0.346 (t[DF19] = 2.404, p = 0.027).[4]

We feel that the presence of some emboli in other distributions and the symmetry of the WMHs showed that the presence of plaque instability not only suggests ipsilateral emboli but also represents a marker of advanced systemic large- and small-vessel disease.

We did not expect to see such a profound relationship between strain and cognitive decline in the present study since we only studied patients who were clinically asymptomatic. Although we did not see the degree of significance that was seen in the prior nonselected patients, we were surprised nonetheless to see that these patients, who were asymptomatic by classic criteria, not only exhibited a decrease in cognitive function, which correlated to strain or instability in the CA plaque, but also showed a surprising amount of WMH and TCD hits compared with controls.

This finding suggests that these plaques do indeed have a surprisingly high degree of instability even though the patients were classically asymptomatic. Ischemic cerebrovascular events are a complex process that takes place in a milieu of preexisting small- and large-vessel diseases. To highlight only large-vessel stenosis is to underestimate the importance of these other factors or comorbidities that take place. Experience has shown that the degree of stenosis is an inadequate screen for patients at risk without gross motor, speech, or visual symptoms. By incorporating parameters that assess large- and small-vessel disease as well as the presence or absence of physical instability in the plaque, we may work toward a better assessment of at-risk patients.

The limitations of this study are primarily in its sample size. We have chosen to carefully identify and clarify cognitive function in a small subset of asymptomatic patients with significant CAS and to carefully study their plaque stability characteristics and cognition over time. We have shown that the addition of more patients does not change the positive result. One of the major problems with this field has been the inconsistency of diagnosis in asymptomatic disease. As our result show, when asymptomatic patients with significant CAS have significantly unstable plaques, they are cognitively impaired. This would make the argument that the present limitations are primarily the classic definition of asymptomatic disease, which emphasizes motor, vision, and speech. We believe that the emphasis on cognition is the major strength of this study, as is the ability to detect the strain changes in the plaque and significantly relate them to cognitive decline.

Conclusions

This study shows that, in classically asymptomatic patients with significant atherosclerotic plaques at the CA bifurcation, a TCD measure of the instability or strain with pulsation within that plaque correlates directly with vascular cognitive decline. The findings further suggest that such unstable plaques are associated with WMHs and subclinical microemboli.

The most significant information from the study is that rather than simply looking at the degree of stenosis, which has always been only a surrogate for the relative amount of plaque at the bifurcation, we need to, and can, examine the physical instability of the plaque in an attempt to predict the risk of plaque rupture, emboli, and progressive brain damage. Furthermore, that damage, which we call symptoms, must be defined beyond that of pure motor, vision, or speech symptomatology to also include cognitive decline. While studies of patients at the extreme end of the spectrum—those with symptomatic emboli significant enough to have major motor function–related presentations—continue to justify interventions in the individuals with significant plaques at the bifurcation, this is not the case in asymptomatic patients, in whom a careful search for at-risk or unstable plaques would improve patient selection. It is possible that those who do not have symptomatic motor presentations but who do have early cognitive decline may now be diagnosed as to who is at risk based on the presence or absence of physical instability within the plaque. Future studies will examine other genetic and biochemical markers for plaque instability to further define the population that would benefit from intensive medical or surgical interventions to prevent all stroke symptoms, both physical and cognitive. We recommend continued study to move toward a more rational basis of patient selection for intervention in those who are not as yet showing clinical stroke by using physical measures of plaque strain to determine carotid atherosclerotic stability or lack thereof.

Acknowledgments

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Disclosures

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Conception and design: Dempsey, Mitchell, Johnson. Acquisition of data: Varghese, Jackson, Wang, Meshram, Mitchell, Berman, Wilbrand. Analysis and interpretation of data: Dempsey, Varghese, Jackson, Wang, Meshram, Mitchell, Hermann, Berman. Drafting the article: Dempsey, Wilbrand. Critically revising the article: Dempsey, Mitchell, Johnson, Wilbrand. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Dempsey. Statistical analysis: Jackson, Wang, Mitchell, Hermann, Johnson, Berman. Administrative/technical/material support: Wilbrand. Study supervision: Dempsey.

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