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● *Original Contribution*

CLASSIFICATION OF SYMPTOMATIC AND ASYMPTOMATIC PATIENTS WITH AND WITHOUT COGNITIVE DECLINE USING NON-INVASIVE CAROTID PLAQUE STRAIN INDICES AS BIOMARKERS

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Abstract—Vascular cognitive decline may be caused by micro-emboli generated by carotid plaque instability. We previously found that maximum strain indices in carotid plaque were significantly correlated with cognitive function. In the work described here, we examined these associations with a larger sample size, as well as evaluated the performance of these maximum strain indices in predicting cognitive impairment. Ultrasound-based strain imaging and cognition assessment were conducted on 75 human patients. Patients underwent one of two standardized cognitive test batteries, either the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) or the National Institute of Neurologic Disorder and Stroke–Canadian Stroke Network (NINDS-CSN) Vascular Cognitive Impairment Harmonization Standards (60 min). Scores were standardized within each battery to allow these data to be combined across all participants. Radiofrequency signals for ultrasound strain imaging were acquired on the carotid arteries using either a Siemens Antares with a VFX 13-5 linear array transducer or a Siemens S2000 with an 18 L6 linear array transducer. The same hierarchical block-matching motion tracking algorithm developed in our laboratory was used to estimate accumulated axial, lateral, and shear strain indices in carotid plaque, with inclusion of adventitia regardless of the ultrasound system and transducer used. Associations between cognitive *z*-scores and maximum strain indices were examined using Pearson's correlation coefficients. Maximum strain indices were also employed to predict cognitive impairment using receiver operating characteristic analysis. All correlations between maximum strain indices and total cognition were statistically significant ($p < 0.05$), indicating that these indices have good utility in predicting cognitive impairment. Maximum lateral strain indices provided an area under the curve of 0.85 for symptomatic patients and 0.68 for asymptomatic patients. Our results indicate the important relationship of maximum strain indices to cognitive function and the feasibility of using maximum strain indices to predict cognitive decline with inclusion of the adventitia layer into the segmentation of plaque. (E-mail: xwang235@wisc.edu or tvarghese@wisc.edu) © 2015 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Elastography, Elasticity imaging, Strain imaging, Carotid Plaque, Motion tracking, Multi-level, Adventitia, Vascular cognitive impairment.**

INTRODUCTION

Stroke is the leading cause of serious, long-term disability and the fourth leading cause of mortality in the United States (Kochanek et al. 2011). Stroke etiologies and vascular risk factors differ between young adult patients and older patients, and mortality or clinical outcome is not independently associated with age (Arnold et al. 2008). Silent strokes, without clinical symptoms, may be five times more prevalent, and are associated with cognitive impairment (Elias et al. 2004; Vermeer et al. 2003). Studies have indicated that the risk of silent stroke is positively related to the extent of carotid stenosis for both symptomatic and asymptomatic patients (Norris and Zhu 1992). Silent stroke and

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cognitive decline may occur with concurrent subclinical emboli (Dempsey et al. 2010), which can flow into the vasculature of the brain and lead to ischemic events resulting in stroke, vascular cognitive impairment or both (Whisnant et al. 1990).

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph et al. 1998) has been widely used as a cognition test protocol in assessment of cognitive impairment. The RBANS takes less than 30 min to administer and evaluates five cognitive domains. This test battery is effective at both characterizing cognitive decline in older patients and screening for dementia in younger patients (Randolph et al. 1998). In addition, age- and education-corrected norms have been provided (Duff et al. 2003). More recently, the National Institute of Neurological Disorder and Stroke–Canadian Stroke Network (NINDS-CSN) published the Vascular Cognitive Impairment Harmonization Standards (Hachinski et al. 2006). Like the RBANS, the 60-min battery recommended by the NINDS-CSN captures several functional domains. These testing standards have been used to assess vascular cognitive impairment (Gorelick et al. 2011), and have been incorporated into standardized stroke patient care with proven clinical feasibility (Han et al. 2014).

Cognitive impairment may be related to cerebral micro-emboli (Russell 2002). Emboli might be generated from rupture of vulnerable plaques—a thin fibrous cap or fissured cap covering the foamy or necrotic core, with the presence of overt hemorrhage, ulceration or thrombus (Stary 1992; Stary et al. 1995); thus, it is clinically important to assess plaque vulnerability (Carr et al. 1996). Ultrasound elastography has been gaining more recognition in plaque characterization, as increased deformation and strain in the plaque have been associated with cognitive decline through embolization (Rocque et al. 2012; Varghese 2009; Wang et al. 2014). Majdouline et al. (2014) investigated the condition of the plaque and found that the absolute value of the associated shear strain elasticity index (SSE) was statistically higher in plaques with increased vulnerability. Mercure et al. (2014) corrected the underestimation of axial strain in plaques using a kinematic constraint-based local angle compensation method. Using clinical findings from high-resolution magnetic resonance imaging (MRI), Naim et al. (2013) found that strain index can index the presence of a lipid core with high sensitivity and moderate specificity. Liu et al. (2015) recently used two-level, radiofrequency (RF) data-based real-time tissue elastography (RTE) to identify vulnerable carotid atherosclerotic plaques. They found that ultrasonic RTE has the potential to characterize composition of carotid plaques *in vivo* and identify plaques that are vulnerable to rupture. Ramnarine et al. (2014) recently conducted a study involving 81 patients in whom they used shear wave elastography (SWE) to quantify carotid plaque elasticity and provide clinically relevant information to help identify unstable carotid plaques. Widman et al. (2015) compared shear moduli of hard and soft plaques in vessel phantoms measured using SWE with mechanical testing results and validated the feasibility of characterizing *in vivo* carotid plaque using SWE. Korukonda et al. (2013) studied sparse-array elastography and compared it with plane-wave imaging and compounded-plane-wave imaging on simulated vessel and vessel phantoms. They concluded that the performance of sparse-array imaging was comparable to that off plane-wave and compounded-plane-wave imaging on phantoms. Hansen et al. (2014) recently extended their strain compounding technique to plane wave-based ultrafast ultrasonic imaging.

In our laboratory, a robust strain estimation algorithm using a hierarchical framework was developed to estimate accumulated strain indices over a cardiac cycle in carotid plaque (McCormick et al. 2012). Accumulated axial and lateral strain indices were found to be capable of assessing vulnerability of carotid plaque in human patients and were significantly correlated with cognitive impairment (Shi et al. 2008; Wang et al. 2014) and increases in white matter hyperintensities (WMH), which are bright regions on T2-weighted brain MRI caused by cumulative subclinical microvascular injury (Berman et al. 2015). We also recently illustrated that shear strain indices obtained with inclusion of the adventitial layer significantly correlated with cognitive function in human patients (Wang et al. 2016). In the work described here, we combined a newer group of patients with the earlier group on which we had reported to obtain a larger sample size and, therefore, increase statistical power, and evaluated the correlation between strain indices and cognitive function, as well as the feasibility of using strain indices to classify cognitive impairment.

METHODS

Data acquisition

Ultrasound imaging and cognition tests were performed on 75 patients (44 male and 31 female) who presented with significant plaque before carotid endarterectomy (CEA) at the University of Wisconsin—Madison Hospitals and Clinics. All enrolled patients met surgical guidelines for CEA with >60% stenosis of the carotid artery based on the North American Symptomatic Carotid Endarterectomy Trial (NASCET 1991) and Asymptomatic Carotid Artery Stenosis (ACAS 1995) criteria. Symptomatic patients presented with classic stroke symptoms such as motor and/or language deficits or transient ischemic attacks