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The relationship between carotid artery plaque stability and white matter ischemic injury

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ABSTRACT

Higher local carotid artery strain has previously been shown to be a characteristic of unstable carotid plaques. These plaques may be characterized by microvascular changes that predispose to intraplaque hemorrhage, increasing the likelihood of embolization. Little is known however, about how these strain indices correspond with imaging markers of brain health and metrics of brain structure. White matter hyperintensities (WMHs), which are bright regions seen on T2-weighted brain MRI imaging, are postulated to result from cumulative ischemic vascular injury. Consequently, we hypothesized that plaques that are more prone to microvascular changes and embolization, represented by higher strain indices on ultrasound, would be associated with an increased amount of WMH lesion volume. This relationship would suggest not only emboli as a cause for the brain degenerative changes, but more importantly, a common microvascular etiology for large and small vessel contributions to this process. Subjects scheduled to undergo a carotid endarterectomy were recruited from a neurosurgery clinic. Prior to surgery, participating subjects underwent both ultrasound strain imaging and brain MRI scans as part of a larger clinical study on vascular health and cognition. A linear regression found that maximum absolute strain and peak to peak strain in the surgical side carotid artery were predictive of WMH burden. Furthermore, the occurrence of microembolic signals monitored using transcranial Doppler (TCD) ultrasound examinations also correlated with increasing lesion burden. It is becoming increasingly recognized that cognitive decline is often multifactorial in nature. One contributing extra-brain factor may be changes in the microvasculature that produce unstable carotid artery plaques. In this study, we have shown that higher strain indices in carotid artery plaques are significantly associated with an increased WMH burden, a marker of vascular mediated brain damage.

1. Introduction

Estimates of carotid stenosis (progressive occlusion of the carotid artery with atherosclerotic plaque) in the general population range from 0–7.5%, with the prevalence increasing drastically with age (de Weerd, 2010). Carotid atherosclerosis is a major precipitant of both symptomatic and asymptomatic (silent) strokes, with an estimated 7–18% attributable to this particular pathology (Petty, 1999; Rubin, 2014; White, 2005). The mechanism is commonly the release of emboli from plaque developing in the walls of the carotid artery (Rothwell, 1996). Some plaques have greater inherent instability, and are thus more likely to release emboli that enter into the brain vasculature (Kwee, 2008). One method to further characterize the stability of plaques is ultrasound elastography (Ophir, 1991; Varghese, 2009). This modality, although

Abbreviations: WMH, white matter hyperintensity; HITS, high intensity transient signals.

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developed over 20 years ago, has only recently come to be utilized in clinical practice, specifically in vascular imaging (Varghese, 2009). Newly developed methods in our laboratory, using a hierarchical block motion tracking algorithm, have increased the efficiency and accuracy of strain analyses (McCormick, 2012). Normal and abnormal tissues display markedly different properties on ultrasound elastography, notably disparate strain parameters (Ophir, 1991; Varghese, 2009).

Higher carotid artery strain has been shown to be a characteristic of unstable carotid plaques that are more likely to embolize (Wang, 2014a). Atherosclerotic vessels with lipidic plaque tend to have higher strain than vessels with calcified plaque, with the degree of strain within individual parts of the plaque varying based on composition, which can be determined using ultrasonic methods (Ribbers, 2007; Shi, 2007, 2008a, 2009). It has been suggested that plaques that are physically unstable during pulsation are more prone to releasing emboli during the cardiac cycle, and thus may be an important contributor to silent strokes (Dempsey, 2010). These unstable, lipidic plaques, as opposed to calcified plaques, undergo greater deformations during the cardiac cycle, which are manifested as higher strain measurements during ultrasound strain imaging (Dempsey, 2010). Non-calcified, hypoechoic plaques have been shown to present with more than 20% accumulated axial strain during a cardiac cycle, whereas more calcified, firmer plaques present with approximately 5% of accumulated axial strain (Shi, 2008b). In fact, this research has been extended by our laboratory to show that higher strain values, both absolute maximum strain and peak-to-peak strain, are associated with indices of decline in global cognitive performance (Wang, 2014a, 2014b; Rocque, 2012). Little is known, however, about how these strain measurements correspond with imaging markers of brain health.

White matter hyperintensities (WMHs), which are bright regions seen on T2-weighted brain MRI imaging, are postulated to result from cumulative ischemic vascular injury. Approximately 50% of individuals will have some degree of WMH by age 40, and by the mid-60s, the majority of adults have WMH observable on imaging (Wen, 2009; Wen and Sachdev, 2004). Vascular risk factors, such as hypertension, atrial fibrillation, and increased intima–media arterial thickness, positively correlate with increased WMH lesion burden (Casado Naranjo, 2015; Knopman, 2011; Alosco, 2013). WMHs have been shown to be positively associated with the degree of cognitive decline, specifically reduced cognitive speed and flexibility (Birdsill, 2014). A community based sample of over 700 healthy adults found that increased WMH lesion burden was associated with poorer performance on executive function tasks (Brickman, 2011). Thus, it is important to investigate the relationship between carotid artery disease, a prevalent public health issue, with that of imaging markers of vascular mediated brain damage.

The degree of carotid stenosis in a population with high grade occlusion (70–99%), with an average age of 69.1 years, appeared to be positively correlated with the total WMH lesion burden (Enzinger, 2010). Furthermore, a study of patients with recent acute lacunar infarcts (average age 56.2 years), found that the extent of carotid disease was associated with a particular increase in periventricular WMH (Kandiah, 2014). In fact, Kandiah and colleagues suggest that the presence of periventricular WMH on imaging should prompt clinicians to examine for the presence of significant carotid vascular disease, and not just attribute the increase in WMH to small vessel intracranial pathology. Other researchers have not found that stenosis correlates with the volume of WMH, but rather that other metrics have significant associations with lesion burden. It may be that it is not the stenosis per se but rather the instability of the plaque that predicts lesion burden. In a population with an average age of 70.2, who have a history of transient ischemic attack or amaurosis fugax (painless, monocular vision loss), and a stenosis of at least 30%, intraplaque hemorrhage, another metric of plaque instability, is significantly associated with WMH lesion burden (Altaf, 2008).

Arterial stiffness measurements have recently been shown to correlate with increased white matter changes in the brain. In a comparative study of patients (average age 53.2) with and without ischemic leukoaraiosis, patients with increased white matter disease had higher strain and pulse wave velocity measurements in the carotid artery (Turk, 2015). In that study, however, patients with unstable carotid plaques or greater than 50% stenosis were excluded (Turk, 2015). Since unstable plaques are believed to embolize at a higher rate than more stable plaques, we sought to determine how plaque stability is associated with WMH lesion volume in a sample of patients scheduled to undergo carotid endarterectomy for treatment of their carotid vascular disease. We hypothesized that plaques that are more unstable, represented by higher strain measurements on ultrasound and more prone to embolization, would be associated with an increased amount of white matter injury, represented by WMH lesion volume, on MRI.

2. Methods

2.1. Participants

Subjects scheduled to undergo clinically indicated carotid endarterectomy for carotid disease were recruited into an investigational multimodal research protocol from neurosurgery clinics and inpatient units at a tertiary care medical center in Madison, WI. Clinical indications were based on those proposed by the ACAS or NASCET trial criteria (Biller, 1998). Patients provided informed consent using a protocol that received prior approval by the University of Wisconsin — Madison institutional review board. Before surgery, subjects (N = 26, 15 males, 11 females, average age 70.27 years) underwent brain MRI imaging, ultrasound strain imaging and medical examinations.

2.2. Ultrasound strain imaging

Ultrasound Radiofrequency (RF) data were acquired using a Siemens S2000 system using an 18L6 linear array transducer (Siemens Ultrasound, Mountain View, CA, USA). The transmit center frequency of the transducer was 11.4 MHz with a single transmit focus set at the depth of the plaque. The ultrasound transducer was positioned to scan the internal carotid artery, however, plaque might extend to the bifurcation in the ultrasound images. RF data over two cardiac cycles were obtained, and plaque regions were segmented at end-diastole using the Medical Imaging Interaction Toolkit (MITK). A hierarchical block-matching motion tracking algorithm was utilized to estimate the accumulated axial, lateral and shear strain distribution in plaques over two cardiac cycles. Maximum and peak-to-peak strain indices were calculated from the strain images.

Successful utilization and reproducibility of ultrasound based strain imaging depend on the estimation of deformation and thereby local strains within the carotid artery wall with high spatial resolution, signal-to-noise ratio (SNR) and over a large dynamic range, while minimizing signal decorrelation and noise artifacts (Varghese and Ophir, 1997; Varghese, 2001). Briefly, this study uses a robust and multi-level hierarchical block matching method for improved strain estimation that incorporates several advances in deformation tracking and displacement estimation (McCormick, 2012). For example, in multi-level methods, local displacements are estimated from a coarse to fine scale, by re-estimating and refining local displacements based on prior information obtained at coarser scales to improve spatial resolution (Shi and Varghese, 2007). A three-level image pyramid was utilized with the hierarchical algorithm to improve computational efficiency (McCormick, 2012; Shi and Varghese, 2007). Discontinuous motion of the artery wall was also addressed in these algorithms (Shi and Varghese, 2007). A dynamic frame skip concept was utilized to ensure that sufficient deformation was always present between the pre- and post-deformation frames processed over a cardiac cycle enabling a smaller frame skip during systole, and a larger frame-skip during end diastole (Daniels and Varghese, 2010). This step improved efficiency of the strain estimation