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● *Original Contribution*

HISTOPATHOLOGIC VALIDATION OF GRAYSCALE CAROTID PLAQUE CHARACTERISTICS RELATED TO PLAQUE VULNERABILITY

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Abstract—Inflammation and angiogenesis play major roles in carotid plaque vulnerability. The purpose of this study was to determine whether gray-scale features of carotid plaques are associated with histologic markers for inflammation. Thirty-eight individuals completed a dedicated research carotid ultrasound exam before carotid endarterectomy. Gray-scale analysis was performed on plaque images to measure plaque echogenicity (gray-scale median [GSM] pixel brightness), plaque area, presence of discrete white areas (DWAs) and the percent of black area near the lumen on any one component of the plaque. Plaques with higher ultrasound GSM had greater percent calcification ($p = 0.013$) on histopathology. Presence of an ultrasound DWA was associated with more plaque hemosiderin ($p = 0.0005$) and inflammation ($p = 0.019$) on histopathology examination. The percent of plaque black area in any one component was associated with a higher score for macroscopic ulceration ($p = 0.028$). Ultrasound plaque characteristics (GSM, DWAs and black areas) represent histopathologic markers associated with plaque vulnerability. ClinicalTrials.gov identifier: NCT02476396. (E-mail: ccm@medicine.wisc.edu) © 2016 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Carotid plaque, Vulnerable plaque, Ultrasound gray-scale imaging.**

INTRODUCTION

Treatment options for patients with carotid artery atherosclerosis are largely influenced by the presence of clinical symptoms and medical imaging estimates of the degree of stenosis and plaque surface characteristics (Brott et al. 2011; Dempsey et al. 2010; Liapis et al. 2009; Ricotta et al. 2011; Salem et al. 2014). However, these criteria do not account for cumulative arterial damage that can lead to clinically unrecognized (silent) strokes caused by the presence of vulnerable plaques and microemboli (Dempsey et al. 2010). It is estimated that for every clinical stroke diagnosis there are approximately five silent strokes that go unnoticed and are associated with cognitive decline, especially in executive function skills (Dempsey et al. 2010; Rocque et al. 2012; Seshadri 2006; Wang et al. 2013). Therefore, better ways to evaluate plaque vulnerability are essential to optimize patient treatment and management, not only to prevent major strokes but also to delay cognitive impairment due to arterial injury.

Vulnerable plaques are associated with thin fibrous caps, large lipid cores, intraplaque hemorrhage, inflammation (Fleiner et al. 2004; Marnane et al. 2014; Salem et al. 2013; Salem et al. 2014; Stary et al. 1995) and in some reports calcification (Shaalan et al. 2004). Ultrasound methods used to assess carotid plaque for features of vulnerability include (i) integrated backscatter (IBC)

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(Bridal et al. 2000; Kawasaki et al. 2001; Nagano et al. 2008), (ii) midband, slope and intercept values of straight-line fit (MBF) to the apparent backscatter transfer function (Waters et al. 2003), (iii) carotid strain imaging (Maurice et al. 2005; Shi et al. 2008; Shi et al. 2009; Wang et al. 2013; Wang et al. 2016a; Wang et al. 2016b), (iv) acoustic radiation impulse force imaging (ARFI) based approaches (Czernuszewicz et al. 2015), (v) shearwave elastography (Garrard et al. 2015) and (vi) gray-scale analyses of plaque features (El-Barghouty et al. 1996; Grogan et al. 2005; Salem et al. 2014; Tegos et al. 2000). IBC, MBF, zero frequency intercept and carotid strain imaging use the raw radiofrequency echo signal to determine associations between scattering properties of the plaque tissues and plaque composition. In gray-scale analyses, B-mode ultrasound images are digitized and processed with specialized software to calculate a gray-scale median (GSM) value and to predict pixel brightness distribution based on the gray-scale value of groups of pixels (Lal et al. 2002; Nicolaides et al. 2010). Images are normalized with blood as the reference for black and the vessel wall (adventitia) as the reference point for white. Comparing pixel brightness values to histology specimens allows for determination of what type of tissue is most likely composing a plaque. Lal et al. (2002) imaged volunteers and patients undergoing carotid endarterectomy (CEA). Volunteers were scanned to determine pixel brightness values of bone (utilizing the tibial head and cranium), fat (utilizing the subcutaneous fat of the abdomen), muscle (biceps muscle) and fibrous tissue (iliotibial tract). A blood vessel was imaged in the same frame as each different tissue types so that the images could be normalized, with blood represented by a gray-scale value of 0 and adventitia represented by a gray-scale value of 190. Patients undergoing CEA had their plaques analyzed, and the pixel brightness distribution was compared to values attained in normal tissue of volunteers and histopathology specimens. Findings showed good agreement with ultrasound gray-scale values predicting the type of tissue present in plaques (*i.e.,* calcium, blood, lipid and fibrous tissue), with a significantly higher amount of blood and lipid associated with symptomatic plaques as compared with asymptomatic plaques ($p = 0.0048$ for blood, and $p = 0.026$ for lipid) (Lal et al. 2002). Evaluation of plaque surface characteristics have also been utilized to characterize features of plaques associated with vulnerability (Kanber et al. 2013a). Kanber et al. (2013a) use a plaque surface irregularity index to objectively quantify plaque surface irregularities. The authors found that plaques with a higher surface irregularity index were associated with ipsilateral cerebrovascular symptoms (Kanber et al. 2013a).

Gray-scale findings that have been associated with plaque vulnerability are (i) low GSM values (Ibrahimi et al. 2014; Nicolaides et al. 2010; Ruiz-Ares et al. 2011; Ruiz-Ares et al. 2014), (ii) juxtaluminal black area (JBA) size (Griffin et al. 2010; Kakkos et al. 2013), (iii) discrete white area (DWA) presence (Nicolaides et al. 2010) and (iv) large plaque area (Nicolaides et al. 2010; Salem et al. 2014). Although studies using these parameters have shown correlations between low echogenicity and worrisome histopathologic plaque features (Salem et al. 2014), few have described how gray-scale features are associated with inflammation (Griffin et al. 2010; Kakkos et al. 2013; Kanber et al. 2015; Nicolaides et al. 2010; Salem et al. 2014), except when ultrasound contrast agents are used (Hjelmgren et al. 2014; Shah et al. 2007). The purpose of this study was to determine whether gray-scale features of carotid plaques are associated with histologic markers for inflammation.

METHODS

Participants

Patients were recruited to participate in the Structural Stability of Carotid Plaque and Symptomatology (NIH funded study: R01 NS064034) study from 2010–2015. This study was approved by the University of Wisconsin Health Sciences institutional review boards and all patients provided informed consent. All patients met criteria for surgical carotid endarterectomy: (i) >60% carotid arterial stenosis (percent stenosis determined by computed tomography angiography, magnetic resonance angiography or ultrasound imaging); and (ii) symptomatic patients had symptoms of motor and/or language deficits on examination and asymptomatic patients had no deficits but may have had silent strokes seen on imaging (North American Symptomatic Carotid Endarterectomy Trial [NASCET] Steering Committee 1991; North American Symptomatic Carotid Endarterectomy Trial Collaborators [NASCET] 1991; Walker et al. 1995). Patients were recruited from the neurosurgery clinics and inpatient units. Potential participants were excluded if they had prior carotid artery surgery, prior carotid artery endovascular procedures or prior cervical radiation, or were otherwise deemed unsuitable for carotid endarterectomy. Thirty-eight patients completed the ultrasound research clinical imaging session and had pathology results available for comparison at the time of this analysis.

Ultrasound imaging

Ultrasound images were acquired on average (standard deviation) 10.6 (13.8) d before carotid endarterectomy. The clinical imaging portion of the protocol was performed with an Acuson S2000 ultrasound system (Siemens Medical Solutions USA, Inc., Malvern, PA, USA) and 9 L4 transducer (Siemens Medical Solutions,

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