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● *Original Contribution*

TRANSCRANIAL DOPPLER AND MICROEMBOLI DETECTION: RELATIONSHIPS TO SYMPTOMATIC STATUS AND HISTOPATHOLOGY FINDINGS

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Abstract—The purpose of this study was to determine the relationship between symptomatic status, transcranial Doppler (TCD) microemboli presence and plaque histopathology findings. TCD was performed on 60 patients (37 symptomatic, 23 asymptomatic) before undergoing clinically indicated carotid endarterectomy. The frequency of microemboli signals was not significantly different between symptomatic and asymptomatic subject groups ($p = 0.88$) and there were no differences observed in the macroscopic or histopathology scoring of these plaques (p-values all > 0.05). The presence of microemboli was associated with an ulceration score (regardless of symptomatic or asymptomatic status, $p = 0.034$), with a one-level increase in ulceration rating associated with an odds ratio of 5.86 (95% [CI] 1.55, 43.4). These findings suggest that both symptomatic and asymptomatic patients may have plaque with similar features of instability and ability to create emboli. Thus, identifying new ways to measure plaque instability may provide important information for optimizing treatment to prevent future stroke. (E-mail: ccm@medicine.wisc.edu) **© 2017 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Ultrasound, Transcranial Doppler, Microemboli, High intensity transient signals (HITS).**

INTRODUCTION

Stroke is the fifth leading cause of death in the United States and the leading cause of long-term disability (Benjamin et al. 2017; Go et al. 2013). It is estimated that for every clinically recognized stroke 5 silent strokes occur (Dempsey et al. 2010; Rocque et al. 2012). This results in approximately 11,000,000 silent strokes per year (Dempsey et al. 2010, 2017; Smith et al. 2000; Smith et al. 2017; Snowdon et al. 1997). Silent strokes are often detected on brain imaging examinations and, although individuals do not present with the classic stroke symptoms (*e.g.,* numbness, muscle weakness, difficulty speaking, ocular changes, *etc.*), they may demonstrate cognitive decline, especially in their executive function (Dempsey et al. 2017; Jackson et al. 2016; Rocque et al. 2012). Symptomatic and asymptomatic individuals, with advanced carotid atherosclerosis, do show significant cognitive decline relative to controls (Dempsey et al. 2017; Jackson et al. 2016). This finding is important in that accelerated cognitive decline may be just as debilitating as clinical stroke, as it can lead to loss of independence and employment (Jackson et al. 2016).

Current clinical examination criteria do not evaluate for cognitive decline (Dempsey et al. 2017; Jackson et al.

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Conflicts of Interest: Dr. Mitchell: Other; may receive future royalties from Davies Publishing, Inc, for authoring two echocardiography textbooks currently under review. She may receive future royalties from Elsevier, Wolters Kluwer, for authoring textbook chapters. Dr. Varghese: Other; receives no financial benefit from Siemens Ultrasound, Research Agreement for use of Ultrasound Research Interface. Dr. Cook is a Consultant and/or on the Advisory Boards of the following: GlaxoSmithKline, Bristol-Myers Squibb, Merck and Mast Therapeutics.

2016). Carotid atherosclerosis is thought to contribute to ischemic stroke and cognitive impairment through (i) cerebral ischemia from flow limiting lesions and/or (ii) release of microemboli from vulnerable plaques (Demarin et al. 2012; Dempsey et al. 2010, 2017; Stork et al. 2002; Sztajzel et al. 2006). Vulnerable plaques are those that are at high risk for rupture, which can result in stroke or transient ischemic attach (TIA) (Salem et al. 2014). Plaque features most often associated with rupture are a thin fibrous cap, large lipid core, inflammation and intra-plaque hemorrhage (Salem et al. 2014). The cumulative effect of the release of these small emboli from a vulnerable plaque can result in cognitive impairment and brain damage (Demarin et al. 2012; Dempsey et al. 2010; Purandare et al. 2006). One method proposed to monitor the propensity of plaque to release of emboli is transcranial Doppler (TCD).

TCD is able to detect high intensity transient signals (HITS) suggestive of microemboli (Altaf et al. 2014; Babikian et al. 1994; Markus and Brown 1993; Markus et al. 2010; Siebler, et al. 1993, 1994; Spencer et al. 1990). HITS, as detected by TCD, are thought to be associated with carotid plaque instability and symptoms related to motor, sensory, visual and speech deficits from stroke and/or TIA (Dempsey et al. 2010; Stork et al. 2002). The frequency of HITS in patients with carotid stenosis varies (Mandani et al. 2011; Siebler et al. 1993), with many studies reporting that individuals with cerebrovascular symptoms have a higher incidence of HITS (Salem et al. 2011; Stork et al. 2002; Sztajzel et al. 2006; Tegos et al. 2001). Such cerebrovascular symptoms may include, stroke, which may present with visual deficits (*e.g.*, amarousis fugax, *etc.*), sensory deficits (*e.g.,* numbness of an extremity, *etc.*), motor deficits (*e.g.*, paralysis, muscle weakness, *etc.*), speech deficits (*e.g.*, difficulty speaking, *etc.*) or TIA (Dempsey et al. 2010; Shintani et al. 2000; Wu et al. 2014).

Carotid plaque morphology also plays a role in plaque stability, especially if ulceration is present (Sztajzel et al. 2006). Plaque ulceration refers to an uneven plaque surface caused by a defect in the endothelium. Clots can adhere to the irregular surface of the plaque, causing the release of microemboli or thrombosis (Miskolczi et al. 1996; Svindland and Torvik 1988). Ulceration is more prevalent in persons with symptomatic cerebrovascular disease compared with asymptomatic individuals (Sitzer et al. 1995; Stork et al. 2002). However, asymptomatic patients have findings, such as silent stroke (Dempsey et al. 2010; Rocque et al. 2012) and cognitive decline (Dempsey et al. 2017). These asymptomatic individuals, therefore, may have plaques that are unstable or not as stable as previously described. Furthermore, the standard clinical examination does not assess the sequeli of repeated small emboli and probable differences between symptomatic and asymptomatic plaques. The purpose of this study was to determine the relationship between symptoms, the presence of microemboli and plaque histopathology findings.

METHODS

Participants

Sixty patients scheduled for carotid endarterectomy, were asked to participate in the Structural Stability of Carotid Plaque and Symptomatology study (R01 NS064034 funded by the National Institutes of Health, Bethesda, MD, USA). During 2010–2016 the patients underwent TCD examination as part of the research study protocol. All participants met criteria for clinically indicated carotid endarterectomy (>60% stenosis of the carotid artery on the basis of the guidelines in the North American Symptomatic Carotid Endarterectomy Trials [1991] criteria and in the "Endarterectomy for Asymptomatic Carotid Artery Stenosis" study [1995]). Our study was approved by the University of Wisconsin Health Sciences Institutional Review Boards and all patients provided informed consent.

Transcranial Doppler

The SONARA Digital Bilateral Systems Transcranial Doppler system (Natus, Middleton, WI, USA) was utilized to perform all TCD examinations. The right and left middle cerebral arteries were insonated at a depth of 45–62 mm from the trans-temporal window. Two, 2.0-MHz pulsed-wave transducers were used simultaneously to record the Doppler signals. Emboli detection software on the SONARA Digital Bilateral Systems Transcranial Doppler (Natus) was used to identify HITS suggestive of microemboli. The following criteria, as defined in "Basic Identification Criteria of Doppler Microembolic Signals" (1995), were used to differentiate HITS from artifacts: (i) high intensity signal (detected by the system), (ii) unidirectional signal within the Doppler velocity spectrum, (iii) a short duration signal (<300 ms) and (iv) the presence of an audible noise (heard as a crackle, thud, chirp or moan). In addition, we also utilized the complex mode to identify high frequency oscillations associated with a moving embolus (see Fig. 1). All patients had at least one HIT satisfying four out of the five criteria present to distinguish a HIT suggestive of a microemboli from an artifact. A physician and two observers reviewed all HITSs on the basis aforementioned criteria to distinguish HITS suggestive of microemboli from artifacts (Berman et al. 2015; Dempsey et al. 2017). The examination was considered positive for the presence of microemboli if one or more HITSs were identified during the TCD monitoring period (Berman et al. 2015; Dempsey et al. 2017).