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● *Original Contribution*

QUEST FOR THE VULNERABLE ATHEROMA: CAROTID STENOSIS AND DIAMETRIC STRAIN—A FEASIBILITY STUDY

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Abstract—The Bernoulli effect may result in eruption of a vulnerable carotid atheroma, causing a stroke. We measured electrocardiography (ECG)-registered QRS intra-stenotic blood velocity and atheroma strain dynamics in carotid artery walls using ultrasonic tissue Doppler methods, providing displacement and time resolutions of 0.1 μm and 3.7 ms. Of 22 arteries, 1 had a peak systolic velocity (PSV) >280 cm/s, 4 had PSVs between 165 and 280 cm/s and 17 had PSVs <165 cm/s. Eight arteries with PSVs <65 cm/s and 4 of 9 with PSVs between 65 and 165 cm/s had normal systolic diametric expansion (0% and 7%) and corresponding systolic wall thinning. The remaining 10 arteries had abnormal systolic strain dynamics, 2 with diametric reduction (>−0.05 mm), 2 with extreme wall expansion (>0.1 mm), 2 with extreme wall thinning (>−0.1 mm) and 4 with combinations. Decreases in systolic diameter and/or extreme systolic arterial wall thickening may indicate imminent atheroma rupture. (E-mail: kwbeach@usa.net) © **2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).**

Key Words: **Carotid, Atherosclerosis, Atheroma, Vulnerable plaque, Vasa plaquorum, Vasa vasorum, Strain, Tissue Doppler.**

INTRODUCTION

The purposes of this study were to: (i) identify carotid artery segments with luminal paradoxical pulsation (systolic peri-stenotic diameter reduction) and (ii) differentiate regions of the arterial wall that exhibit compressible strain indicating the presence of pathologic neovascular vasa vasorum and vasa plaquorum. We postulate that: (i) carotid arterial atheromas are not incompressible, but instead include a dynamic, composite neovascular tissue allowing for intra-atheroma vascular volume changes during periods of adverse transmural pressure, and (ii) these neovascular regions are vulnerable to rupture (Feinstein 2006; Lal et al. 2011; Sun 2014). This transcutaneous ultrasound method for differentiating vulnerable from benign carotid atheromas might allow appropriate, in-time, targeted, prophylactic carotid revascularization therapy.

Atheroma rupture is rare, even in the presence of severe carotid stenosis; only 17% of symptomatic patients and 2% of asymptomatic patients with treatable carotid stenosis experience recognizable motor, sensory, or functional symptoms of stroke attributable to the stenosis within 2 y of detection (De Fabritiis et al. 2002) if not revascularizd. In the patients at highest risk, only 2% per year have a stroke (Gardin et al. 2014). In addition to symptomatic stroke, athero-emboli released by atheroma rupture (Bazan et al. 2014a) may stream to other portions of the cerebral cortex causing "silent" infarcts, effects of which are often attributed to aging and dementia rather than embolic infarction.

Clinical studies of carotid therapies to prevent stroke are further hindered by difficulties inherent in differentiating events caused by carotid athero-emboli

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from those caused by thrombo-emboli from sub-aortic sources and athero-emboli from intracranial sources (Derdeyn et al. 2014). Even after revascularization and the exclusion of peri-treatment events, nearly 2% of cases have ipsilateral stroke within 4 y (Bonati et al. 2015; Brott et al. 2010). Intra-atheroma hemorrhage is thought to be an initiating and contributing factor to atheroma rupture leading to intra-arterial emboli (Treiman et al. 2015).

We hypothesized that intra-stenotic pressure alterations are required to initiate the process of atheroma rupture. Changes in intra-arterial flow dynamics result from Bernoulli pressure depression effects produced by atherosclerotic pathology. The presence of intra-atheroma hemorrhage was associated with intra-stenotic velocities greater than 4 m/s measured in pre-surgical examination (Beach et al. 1993). At velocities of 4 m/s, the resulting intra-stenotic pressure depression would exceed 64 mm Hg during systole ($\Delta P = 4V_{max}{}^2$). Such velocities are more likely if collateral blood flow pathways via the circle of Willis are absent (Lal et al. 2011). We postulated that pressure depression >64 mm Hg resulting from intra-vascular atherosclerotic pathology, when combined with a pulse pressure of 40 mm Hg (*i.e.*, BP = 120/80), would cause paradoxical (inverted) intra-stenotic pressure pulsation ($BP_{stenosis}$ = 56/64), a potential harbinger of atheroma eruption. Diametric reduction during systole in severe carotid stenosis has been reported (Bonnefous et al. 2000) and attributed to the Venturi effect (Ramnarine et al. 2003).

Some investigators have used mechanical properties of excised tissue and the stress applied to the atheroma by arterial lumen pressure fluctuations to compute atheroma dynamics. These studies have assumed either linear or non-linear, elastic or plastic tissue properties, but all have considered the tissues to be incompressible (Teng et al. 2014). Other studies of carotid atherosclerosis have compared the presence and characteristics of carotid atheromas with the rate of subsequent stroke or carotid atheroma progression (Nicolaides et al. 2010; Truijman et al. 2014) or past events (van Lammeren et al. 2012). An extreme atheroma expansion event, which may occur when hypertension, arrhythmia and cerebral vasodilation coincide, could lead to atheroma disruption resulting in stroke (Folts 2007).

The vasa vasorum (vasa plaquorum) microvasculature in the atheromatous wall provides a means for the volume of the wall to be changed within each cardiac cycle by the inflow and outflow of blood via the adventitia. The purpose of this study was to measure the dynamic waveform of those volume changes to characterize the pathologic nutritional circulation of the atheroma that may make the atheroma vulnerable to rupture. In addition, we found that in some arteries with high velocity, a paradoxical diametric pulsation (referenced to electrocardiography [ECG]-registered QRS timing) may indicate intimal pressure depression that might facilitate the rupture of the atheroma.

METHODS

Patients scheduled for clinically indicated ultrasound examination of the carotid arteries at the University of Washington Vascular Laboratory were invited to participate in this study. The protocol was approved by the Human Patients Division's institutional review board. Each participating patient signed an approved consent form. No demographic data were gathered; such data were not considered essential to the study hypotheses at the time.

A customized ultrasonic Duplex scanner (Hitachi Hi Vision 5500 system Hitachi Medical System America, Twinsburg, OH, USA) with an EUP-L53 linear-array transducer centered at 7.5 MHz was used to capture three types of data (Fig. 1) from each carotid artery examined, including: (i) one 40-mm-wide 2-D brightness-mode (B-mode) pilot image (Fig. 2); (ii) between 6 and 10 blood Doppler spectral waveforms with simultaneous ECG; and (iii) between 2 and 8 2-D radiofrequency (RF) image panel (6.5-mm-wide) real-time sequences at 270 frames per second using ECG-QRS triggering for tissue Doppler strain data. The 2-D B-mode pilot image was used for anatomic identification and relative spatial registration of the blood Doppler and tissue Doppler data. The ECG-registered QRS complex was used to index the beginning of all time traces, providing temporal alignment within the cardiac cycle. B-Mode, Doppler waveform and RF image panel sequences were acquired sequentially, each involving a different series of cardiac cycles. Therefore, although the first cardiac systole was relatively time registered for analysis, the second displayed cycle often exhibited unavoidable jitter due to natural changes in the QRS-QRS interval during the examination.

Each 2-D RF data panel was captured at a frame rate of 270 Hz beginning at the ECG-QRS trigger and extending for two cardiac cycles. The first frame of the panel series was rendered as a 2-D B-mode image for post-examination manual tracing of arterial wall boundaries. This image was also used to estimate the location of acquisition on the pilot image. The sonographer traced the superficial and deep adventitial and luminal boundaries—$W_1(0)$, $W_2(0)$, $W_3(0)$, $W_4(0)$—on the first frame B-mode image of each panel series (W_1 is the superficial adventitial boundary, W_2 is the superficial intimal wall, W_3 is the deep intimal wall, W_4 is the deep adventitial boundary). These tracings were used as the key locations for RF tracking of the four boundaries in the depth. The autocorrelation method of Rabben et al. (2002) with center frequency correction was used to create a time series, $W_i(t)$, for each beam line from each boundary in each panel series (position vs.