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● *Original Contribution*

ULTRASOUND SPECKLE TRACKING STRAIN ESTIMATION OF *IN VIVO* CAROTID ARTERY PLAQUE WITH *IN VITRO* SONOMICROMETRY VALIDATION

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Abstract—Our objective was to validate a previously developed speckle tracking (ST) algorithm to assess strain in common carotid artery plaques. Radial and longitudinal strain was measured in common carotid artery gel phantoms with a plaque-mimicking inclusion using an in-house ST algorithm and sonomicrometry. Moreover, plaque strain by ST for seven patients (77 ± 6 y) with carotid atherosclerosis was compared with a quantitative visual assessment by two experienced physicians. *In vitro*, good correlation existed between ST and sonomicrometry peak strains, both radially ($r = 0.96$, $p < 0.001$) and longitudinally ($r = 0.75$, $p < 0.01$). *In vivo*, greater pulse pressure-adjusted radial and longitudinal strains were found in echolucent plaques than in echogenic plaques. This illustrates the feasibility of ultrasound ST strain estimation in plaques and the possibility of characterizing plaques using ST strain *in vivo*. (E-mail: erik.widman@sth.kth.se) © 2015 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Carotid artery, *In vitro*, *In vivo*, Phantom, Plaque characterization, Speckle tracking, Strain, Ultrasound, Validation.**

INTRODUCTION

Plaque characterization is critical when determining treatment for patients with carotid atherosclerotic plaque (Mono et al. 2012; Reid 1998). One type of plaque, known as vulnerable plaque, has a high probability of rupture, which causes emboli to break off from the plaque and travel *via* the circulatory system to vessels in the brain. As the arteries become narrow, the emboli can lodge in the vessel wall, restricting blood flow to parts of the brain and causing a temporary transient ischemic attack or permanent embolic stroke (Reckless and Buchan 2008). Plaque characterization in the carotid artery is therefore significant in risk assessment for cerebral ischemic events.

In current clinical practice, ultrasound-based methods for plaque characterization are limited to visual assessment of plaque morphology, hypo-echoic area and echo reflection in the plaque (Gray-Weale et al. 1988; Kakkos et al. 2013) or, more commonly in research, computerized evaluation of echogenic properties (Prahl et al. 2010). Limitations of visual assessment include inter-observer variability, human error and misclassification caused by ultrasound machine settings (Arnold et al. 1999). Other clinical practices for carotid plaque detection include carotid angiography (Armas et al. 1981; Matos et al. 2014), although angiography determines only plaque location and size and does not offer information on plaque composition. Treatment options such as endarterectomy and angioplasty are often based on relative lumen diameter. The accepted criterion for surgical selection of patients with symptomatic carotid artery disease is a stenosis of 70% reduction in relative lumen diameter of the internal carotid artery (Arnold et al. 1999). In certain instances of plaque composition, location and luminary occlusion, surgery poses a higher risk to the patient than non-invasive treatments such as medication (Easton and Wilterdink 1994). Quantitative tools are needed to better assess the likelihood of plaque rupture to determine if invasive treatment options are required, particularly in cases with borderline lumen obstruction.

Plaque characterization has been attempted with a number of imaging modalities and techniques. Magnetic resonance imaging (MRI) has been used to characterize

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plaque, but is expensive and time consuming and can be a high risk factor in initiating recurrent plaque rupture events (Ronen et al. 2007; Teng et al. 2011; Zhao et al. 2013). Saba et al. (2013) attempted to use computed tomography (CT) to characterize plaque based on Hounsfield unit (HU) values, but found that the plaque HU level significantly changed with the kilo-electron volts applied.

Non-invasive ultrasound-based methods include measuring the gray-scale median (GSM) of plaques (Biasi et al. 1999; Kanber et al. 2013a; Salem et al. 2012), although conflicting studies question the effectiveness of the GSM as an indicator of increased risk of stroke (Biasi et al. 2004; Froio and Biasi 2007; Reiter et al. 2006). Furthermore, GSM can vary between different ultrasound machine manufacturers or between different users depending on the ultrasound machine settings. Plaque characterization by scatter size and attenuation coefficient has been attempted, but no *in vivo* studies have been conducted (Shi et al. 2008b). Thermal strain imaging has been used *in vivo* to detect lipids in atherosclerotic plaques in the femoral arteries of rabbits (Mahmoud et al. 2013). Vulnerable carotid plaque has also been detected using contrast-enhanced ultrasound imaging in combination with tissue Doppler imaging (Deyama et al. 2013), but tissue Doppler imaging has been found to be of limited use because of high variability (Ramnarine et al. 2003).

Two new ultrasound-based elastography methods that have been used to characterize plaque are acoustic radiation force impulse (ARFI) imaging (Allen et al. 2011; Dahl et al. 2009) and shear wave elastography (SWE) (Ramnarine et al. 2014; Widman et al. 2012). Acoustic radiation force impulse imaging can readily distinguish between stiff and soft tissue regions, but can only detect relative stiffness differences between the plaque and the nearby surrounding tissue. SWE still needs to be adapted for plaque measurements, as current results have neglected the viscoelasticity of the carotid artery as well as the shear wave phase aberration effects caused by the cylindrical geometry of the vessel.

Atherosclerotic plaque strain is another measure that has been suggested for detection of plaques liable to rupture. Ultrasound-based speckle tracking is a block-matching technique that estimates strain by tracking interference patterns across imaging frames. Ultrasound speckle tracking plaque characterization has been found feasible with intravascular ultrasound (IVUS) (de Korte et al. 2002; Le Floc'h et al. 2012; Schaar et al. 2003). Moreover, there have been attempts to assess plaque strain non-invasively by radiofrequency-based ultrasound speckle tracking (McCormick et al. 2012; Schmitt et al. 2007).

The driving forces of arterial strain are thought to vary with the type of strain. Radial strain and circumferential strain are caused by the blood pressure wave during the cardiac cycle. Given conservation of wall volume, radial strain will have a waveform inverse to the pressure wave and be of similar shape. Longitudinal strain is more complex and thought to be caused by a combination of the pressure wave and conservation of volume, wall shear stress from the blood and tethering of the vessel caused by the contracting heart (Cinthio et al. 2006; Hodis and Zamir 2009).

Even though several plaque characterization techniques have been proposed, non-invasive techniques with extensive validation by independent reference methods are, to the best of our knowledge, still lacking. Of the clinically available imaging modalities, it is advantageous to use B-mode ultrasound to characterize plaque because of its low cost, accessibility and tolerability. Recently, our research group published a speckle tracking algorithm based on block matching that successfully estimated strain in the wall of a carotid artery *in silico* (Larsson et al. 2011a), *in vitro* (Larsson et al. 2011b) and validated *in vivo* in a sheep model (Larsson et al. 2013). The aim of this study was to use this speckle tracking algorithm to validate radial and longitudinal strain assessment in plaques by comparing the speckle tracking measurements with sonomicrometry in tissue-mimicking phantoms. Additionally, this study attempted to preliminarily illustrate the feasibility of *in vivo* plaque strain measurements in patients with atherosclerotic plaques, with the hypothesis that soft vulnerable plaques with a large lipid or intraplaque hemorrhage core should exhibit larger strain compared with more stable fibrous plaques.

METHODS

The in-house strain estimation algorithm was first tested in a phantom setup mimicking the carotid artery and validated with sonomicrometry to ensure the accuracy of the algorithm. Upon validation, *in vivo* ultrasound cine loops were collected for patients with carotid *atherosclerotic* plaques in which the strain was calculated.

In vitro *experiments*

Vessel phantom construction. Four *in vitro* carotid artery phantoms with a plaque-mimicking inclusion were constructed from a mixture (w/w) of 87% de-ionized water, 10% polyvinyl alcohol (PVA) with a molecular weight of 56.140 g/mol (Sigma–Aldrich, St. Louis, MO, USA) and 3% graphite powder with a particle size <50 μm (Merck, Darmstadt, Germany). The solution was heated and stirred until the mixture thickened and was fully dissolved. It was subsequently poured into the vessel phantom mold (Fig. 1a), which consisted of a hollow acrylic block (cylindrical with a 12-mm diameter, 100-mm length