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● *Clinical Note*

RELATIONSHIP BETWEEN PLAQUE ECHO, THICKNESS AND NEOVASCULARIZATION ASSESSED BY QUANTITATIVE AND SEMI-QUANTITATIVE CONTRAST-ENHANCED ULTRASONOGRAPHY IN DIFFERENT STENOSIS GROUPS

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Abstract—The aim of this study was to determine the relationship between plaque echo, thickness and neovascularization in different stenosis groups using quantitative and semi-quantitative contrast-enhanced ultrasound (CEUS) in patients with carotid atherosclerosis plaque. A total of 224 plaques were divided into mild stenosis (<50%; 135 plaques, 60.27%), moderate stenosis (50%–69%; 39 plaques, 17.41%) and severe stenosis (70%–99%; 50 plaques, 22.32%) groups. Quantitative and semi-quantitative methods were used to assess plaque neovascularization and determine the relationship between plaque echo, thickness and neovascularization. Correlation analysis revealed no relationship of neovascularization with plaque echo in the groups using either quantitative or semi-quantitative methods. Furthermore, there was no correlation of neovascularization with plaque thickness using the semi-quantitative method. The ratio of areas under the curve (RAUC) was negatively correlated with plaque thickness ($r = -0.317$, $p = 0.001$) in the mild stenosis group. With the quartile method, plaque thickness of the mild stenosis group was divided into four groups, with significant differences between the 1.5–2.2 mm and ≥3.5 mm groups ($p = 0.002$), 2.3–2.8 mm and ≥3.5 mm groups ($p < 0.001$) and 2.9–3.4 mm and ≥3.5 mm groups ($p < 0.001$). Both semi-quantitative and quantitative CEUS methods characterizing neovascularization of plaque are equivalent with respect to assessing relationships between neovascularization, echogenicity and thickness. However, the quantitative method could fail for plaque <3.5 mm because of motion artifacts. (E-mail: ruanlitao@163.com; rlt555@mail.xjtu.edu.cn) **© 2017 World Federation for Ultrasound in Medicine & Biology. All rights reserved.**

Key Words: **Carotid artery, Contrast-enhanced ultrasound, Neovascularization, Echogenicity, Thickness.**

INTRODUCTION

The most widely accepted predictor of stroke risk is plaque. However, additional imaging features assessing atherosclerotic plaque morphology and composition are being recognized as significant factors (Gallino et al. 2012). Assessment of plaque echo and thickness on B-mode ultrasound has revealed high-risk plaque features (Nighoghossian et al. 2005) associated with a higher risk for stroke (Reiter et al. 2008).

Several lines of evidence indicate that intra-plaque neovascularization is associated with histologic features of vulnerable plaques (Eriksson 2011; Moreno et al. 2004) and clinical symptoms (Fleiner et al. 2004). Contrast-enhanced ultrasound (CEUS) is a valuable imaging tool used to study intra-plaque neovascularization (Clevert et al. 2011). Several groups have developed quantitative and semi-quantitative systems for grading CEUS-detected intra-plaque neovascularization in humans (Akkus et al. 2013; Deyama et al. 2013). Several prospective studies have reported that greater neovascularization on CEUS is associated with hypo-echoic plaques (Moguillansky et al. 2011; Xiong et al. 2009) and clinical symptoms in patients with carotid atherosclerosis (Xiong et al. 2009). On the basis of these studies, CEUS examination combined with plaque echo and thickness measurements may provide a novel imaging technique for carotid atherosclerosis stroke risk stratification (Piscaglia et al. 2012).

Therefore, the aim of this study was to determine the relationship between plaque echo, thickness and neovascularization in different stenosis groups using quantitative and semi-quantitative CEUS in patients with carotid atherosclerosis.

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Table 1. General clinical data*

	Mild stenosis (n = 135)	Moderate stenosis (n = 39)	Severe stenosis (n = 50)	*p* value†
Sex, male	116 (85.92%)	35 (89.74%)	44 (88%)	0.940
Age (y)	66 (59–73)	62 (60–68)	68 (62–77)	0.019
Smoking history, yes	87 (64.44%)	18 (46.15%)	31 (62%)	0.313
Drinking history, yes	24 (17.78%)	4 (10.26%)	2 (4%)	0.017
Hypertension, yes	88 (65.19%)	29 (74.36%)	34 (68%)	0.663
Diabetes, yes	44 (32.59%)	10 (25.64%)	18 (36%)	0.556
Triglycerides (mmol/L)	1.22 (0.96–1.62)	1.11 (1.03–1.25)	1.20 (1.04–1.76)	0.504
Cholesterol (mmol/L)	3.55 (2.97–4.31)	3.38 (2.94–3.81)	3.45 (3.10–4.00)	0.556
HDL-C (mmol/L)	1.09 (0.92–1.27)	1.05 (0.94–1.21)	0.99 (0.87–1.17)	0.268
LDL-C (mmol/L)	1.85 (1.49–2.73)	1.73 (1.52–2.09)	1.88 (1.46–2.46)	0.696
Apolipoprotein a (mmol/L)	1.19 (1.08–1.30)	1.13 (1.07–1.27)	1.16 (1.07–1.31)	0.764
Apolipoprotein b (mmol/L)	0.70 (0.57–0.87)	0.68 (0.57–0.74)	0.67 (0.60–0.83)	0.630
Blood glucose (mmol/L)	5.28 (4.54–6.18)	4.63 (4.28–5.24)	5.81 (4.57–7.34)	0.015
Glycosylated hemoglobin	5.80 (5.50–6.60)	5.90 (5.57–6.72)	6.00 (5.50–7.20)	0.619
Plaque thickness (mm)	2.8 (2.30–3.40)	3.90 (3.10–4.70)	4.05 (3.37–4.80)	0.000
RAUC	0.31 (0.18–0.44)	0.22 (0.13–0.34)	0.25 (0.16–0.35)	0.024

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; RAUC = ratio of areas under the curve.

* Data are expressed as number (%) of patients and median (interquartile range, 25th and 75th percentiles).

† *p* values are for comparisons among the three groups.

METHODS

Patients

Patients with plaques during 2013 and 2017 in our hospital were included in this study. Inclusion criteria were (i) carotid plaques ≥1.5 mm and (ii) no acoustic shadowing of hyper-echoic plaque areas. Exclusion criteria were (i) allergy to contrast agents; (ii) acute coronary syndrome, cardiogenic shock, pulmonary edema, major surgery, trauma or serious infections in the prior 4 wk; (iii) severe liver disease; and (iv) chronic renal failure, serum creatinine levels >2.5 mg/dL or congestive heart failure or a total of five other serious diseases. We enrolled a total of 224 patients, including 195 men (87%; average age, 65 y). We analyzed the thickest plaque on both sides per patient. Clinical characteristics of the patients are summarized in Table 1. Written informed consent was obtained from all patients before the study, which was approved by the institution's human research committee.

Standard ultrasound study of the carotid artery

A standard carotid ultrasound (US) examination was performed in all patients at the screening visit using an 11.0-MHz linear-array transducer (Prosound LOGIQ-E9; GE, Fairfield, CT, USA). According to the Mannheim consensus, atherosclerotic plaque represents a change in the local structure of the invasion of the arterial wall ≥1.5 mm (Touboul et al. 2012). According to the guidelines for blood flow velocity, plaque stenosis was divided into three groups: < 50%, 50%–69% and 70%–99% (Brott et al. 2011). Each type of echo was classified according to Gray–Weale echogenicity grading classification classification criteria (Gray-Weale et al. 1988): uniformly echolucent (class I); predominantly echolucent (class II); predominantly echogenic (class III); or uniformly echogenic or extensively calcified (class IV).

CEUS of the carotid artery

Carotid CEUS studies were performed with the same machine used for the standard studies, with addition of a 9 L probe with a 7-MHz transmission frequency. The mechanical index was reduced to the lowest possible level (0.14), and the time-gain compensation (TGC) was adjusted to provide the highest contrast effect. Image depth was adjusted to 3.0–4.0 cm according to the size of the carotid artery. The focus position was set at the level of the carotid artery. The TGC was adjusted to reduce noise from the wall of the carotid artery and the plaque. All settings were kept constant throughout each examination.

Carotid CEUS was performed using the ultrasound contrast agent Sonovue (Bracco, Milan, Italy) suspended in 5 mL of saline. A bolus of contrast agent (2.0 mL) was injected into the median cubital vein, immediately followed by 5 mL of saline. CEUS clips were recorded using a dual-display mode for simultaneous standard B-mode US and CEUS views. Harmonic ultrasound images were recorded for 10–20 s at baseline and after appearance of the contrast agent in the carotid artery for 120 s. Neovascularization was identified by rapid movement of the echogenic reflectors of the microbubbles within the plaque. The cine clips were stored as AVI files. Patients were asked not to swallow during the recordings.

CEUS in the analysis of plaque neovascularization

Scans were performed and analyzed by two researchers with 5 y of experience in CEUS.