Identification of Patients with a Histologically Unstable Carotid Plaque Using Ultrasonic Plaque Image Analysis

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WHAT THIS PAPER ADDS
If validated, it may be possible to identify patients with a higher or lower likelihood of having a histologically unstable plaque using readily accessible ultrasound images and plaque software analysis.

Objectives: In patients with carotid stenosis the risk of stroke is highest in the first few days after onset of symptoms and it is low in asymptomatic patients. The ability to identify patients with a high (or low) probability of having a histologically unstable plaque might become a complimentary method that can refine the indications for surgical intervention.
Methods: Two histopathologists, using validated American Heart Association criteria, independently graded plaques harvested during carotid endarterectomy. Preoperative Duplex images were independently assessed for juxtaluminal black area, plaque type, plaque area, and grey-scale median (GSM) following image normalization. Logistic regression analysis was then performed to create a model for predicting predominantly histologically unstable or stable plaques.
Results: A total of 126 patients were included in the study. Based on the presence and extent of histological features including haemorrhage, thrombus, fibrous tissue, lipid core, inflammation, neovascularity, foam cells, and cap rupture, 39 plaques were graded as predominantly stable, while 87 were predominantly unstable. Unstable plaques were associated with a plaque area >95 mm^2 (OR 4.15; 95% CI 1.34–12.8 $p = .009$), a juxtaluminal black area >6 mm^2 (OR 2.77; 95% CI 1.24 to 6.17 $p = .01$) and a GSM <25 (OR 3.76; 95% CI 1.14–12.39). Logistic regression indicated that patients with the first two features had a 90% probability of having a histologically unstable plaque. The model was used to calculate the probability of having an unstable plaque in each patient. The receiver operating characteristic curve using the p value was 0.68 (95% CI 0.59–0.78).
Conclusions: Computerized plaque analysis has the potential to identify patients with histologically unstable carotid plaques. This model requires validation, but offers the potential to influence patient selection for emergency interventions and the monitoring of medical therapy.

Article history: Received 30 January 2014, Accepted 7 May 2014, Available online 16 June 2014
Keywords: Carotid, Plaque instability, Ultrasound, Atherosclerosis

INTRODUCTION

Guidelines[1,2] for treating patients with carotid artery disease rely primarily on stenosis severity and clinical symptoms. The majority of strokes in patients with moderate to severe carotid stenoses are caused by thromboembolism from an unstable carotid plaque,[3] defined as having several of the following features: thinned/ruptured cap, large lipid core, intraplaque haemorrhage, surface thrombus, cap/plaque inflammation, and marked neovascularization.[4,5] These features (especially dense macrophage inflammation) were recently shown to be associated with a high risk of early recurrent stroke in patients with 50–99% stenoses, leading the authors to recommend that imaging strategies be developed for identifying patients with unstable plaque features.[6]

Computed tomography (CT),[7,8] magnetic resonance imaging (MRI),[9] positron emission tomography (PET), and infrared spectroscopy[10] have been used to identify the "unstable plaque". Whilst showing reasonable concordance with histological findings, most are not as accessible as ultrasound. In earlier ultrasound studies, hypoechoic plaques (Types 1 and 2) were associated with symptoms.[11,12] More recent studies using ultrasound and plaque characterization

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1078-5884/$ – see front matter
http://dx.doi.org/10.1016/j.ejvs.2014.05.015

following image normalization have identified plaque features that were independent predictors of future cerebrovascular events. It was hypothesized that these might enable risk stratification in patients with asymptomatic carotid stenosis.[13,14] These features included; low grey scale median (GSM), larger plaque area, and the presence/size of the juxtaluminal plaque area. When the same scrutiny was applied to images of plaques from symptomatic patients, it identified a subgroup with a higher rate of recurrent transient ischaemic attacks (TIAs) whilst awaiting surgery.[15]

The aim of this study was to determine the association between ultrasound-derived plaque features and histological plaque instability. We hypothesized that the ability to identify a high (or low) probability of unstable plaque might provide an alternative (and accessible) method for planning the nature and urgency of carotid interventions, as well as being a means of monitoring the effects of medical therapy on plaque morphology in other patient cohorts.

METHODS

Consecutive patients undergoing carotid endarterectomy (CEA) between August 2008 and March 2010 were included after giving informed consent. The study was authorized by the Leicestershire, Northamptonshire, and Rutland Ethics Committee. Patients were included if they were recently symptomatic (<6 months) with a 50–99% NASCET stenosis,[16] or asymptomatic with a 70–99% stenosis.

Symptomatic patients were admitted directly from the daily TIA Clinic or from the Stroke Unit. Symptomatic patients were started on 300 mg of aspirin and 40 mg of simvastatin prior to transfer, and these medications were continued throughout the peri-operative period. In addition, all patients received 75 mg of clopidogrel the night before surgery.[17] A fuller description of the reconfigured TIA clinic has been published elsewhere.[18] CEA was performed as soon as possible after the index event. Asymptomatic patients were started on medical therapy in the outpatient department. Most had been taking aspirin, statin, and antihypertensive therapy for at least 4 weeks prior to surgery.

Duplex imaging

Accredited ultrasonographers performed the duplex examinations using an ATL HDI5000 ultrasound scanner and an L12–5 linear array probe (Philips Medical Systems, Andover, MA, USA). Stenosis severity was measured using NASCET-derived measurement criteria.[16] In addition to grading stenosis severity, B-mode longitudinal unenhanced images of the plaque were obtained with and without colour flow.[14,19] Image analysis was then performed by a single investigator (A.N.) who was completely blinded to all clinical and histological data.

Image normalization and measurements of GSM and JBA (see Fig. 1a,b)

Image analysis was performed using the "Plaque Texture Analysis software" (LifeQ Medical, 66 Metochiou, Engomi, 2407, Cyprus; www.lifeqmedical.com), which is a dedicated software package.[14] Image normalization was performed so that the area representing blood had a grey scale of zero, whilst the brightest area of adventitia had a grey scale of

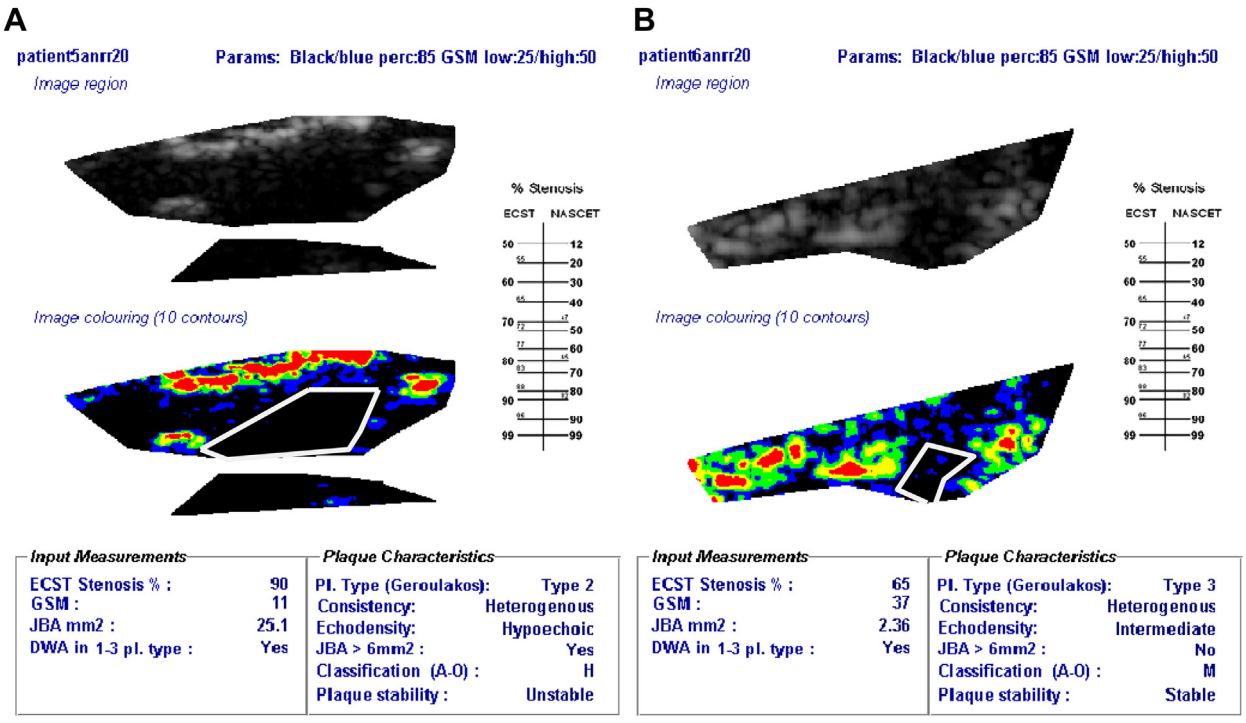

Figure 1. (A) "Unstable" plaque detected on ultrasound analysis. Juxtaluminal black area outlined in white. Discrete white areas (DWAs) are bright red areas within the black lumen. (B) "Stable" plaque features detected on ultrasound analysis. Juxtaluminal black area outlined in white. DWAs are bright red areas within the black lumen.