Detection of Carotid Adventitial Vasa Vasorum and Plaque Vascularization With Ultrasound Cadence Contrast Pulse Sequencing Technique and Echo-Contrast Agent

Edoardo Vicenzini, MD, PhD; Maria Fabrizia Giannoni, MD; Francesco Puccinelli, MD; Maria Chiara Ricciardi, MD; Marta Altieri, MD, PhD; Vittorio Di Piero, MD, PhD; Bruno Gossetti, MD; Fabrizio Benedetti Valentini, MD; Gian Luigi Lenzi, MD

Background and Purpose—Adventitial vasa vasorum and plaque vascularization have been established as predictors of unstable atheromasic lesions in cerebro- and cardiovascular patients. Ultrasound contrast agents provide reliable information on tissue perfusion and microcirculation. We used contrast ultrasound duplex scanning to identify carotid plaque vascularization.

Methods—Contrast carotid duplex scanning was performed in 23 patients with plaques of different degree of stenosis and echogenicity.

Results—Plaque vascularization was detected in the fibrous and fibro-fatty tissue and not observed in the calcific nor in the necrotic and hemorrhagic tissue. Constantly, a small vessel was observed under ulcerations.

Conclusions—Carotid contrast ultrasound imaging appears to be an emerging technique for identifying plaque angiogenesis. Further studies are needed to clarify the role of plaque angiogenesis for assessing cerebrovascular risk and to monitor effects of therapies aimed to plaque remodelling. (Stroke. 2007;38:000-000.)

Key Words: carotid atherosclerosis ■ plaque vascularization ■ ultrasonography ■ echo-contrast agents ■ Cadence CPS technique

Morphological studies with ultrasound have identified echographic plaque characteristics, beyond the severity of stenosis, that reflect a higher risk of vulnerability, so defining the “unstable” plaque. Adventitial vasa vasorum and plaque neovascularization have been well established and confirmed in histological studies as predictors of unstable atheromasic lesions in cerebro- and cardiovascular patients.

CT, MRI, digital angiography and even positron emission tomography have been recently applied to image targets of the biological functional pathways of carotid plaques. Nonetheless, these techniques are expensive, sometimes invasive and not always available in daily practice.

Feinstein reported the first experiences with ultrasound contrast agents (UCA) for identifying carotid plaque vascularization. Recently, we have checked the capability of UCA to identify perfusion and angiogenesis in brain tumors with a new ultrasonographic software already validated for assessing microcirculation and cerebral tissue perfusion in ischemic stroke.

The aim of the present study was to perform contrast carotid duplex scanning in order to identify angiogenesis in carotid plaques with different degree of stenosis and echogenicity.

Materials and Methods

Patients affected by carotid stenosis, asymptomatic for recent cerebrovascular disease and myocardial infarction, and referred to our ultrasound laboratory for elective investigation were randomly enrolled in the study.

Carotid duplex was performed with a Siemens Sequoia 512, equipped with software “Cadence contrast Pulse Sequencing”. Lin-ear array probes (6, 8 and 15 Mhz) with standard presets for all the patients were used.

Plaque morphology has been described according to well-established criteria: hyperechoic with acoustic shadow, hyperechoic, isoechoic, hypoechoic, and consequently calcific, fibrous, fibro-calcific, fibro-fatty, hemorrhagic. Plaque surface as regular, irregular and ulcerated. The degree of stenosis according to European Carotid Surgery Trial (ECST) criteria and to blood flow velocities.

The contrast ultrasound investigation was performed after a bolus injection in an antecubital vein (20 Gauge Venflon) of Sonovue 2.5 mL (Bracco), followed by 10-mL saline flush. The 15-Mhz linear array probe with a mechanical index varying from 0.4 to 1.4, with contrast pulse sequencing continuous real-time recording was used to achieve the best visualization of the plaque morphology and vascularization.

The study was approved by the ethical committee and all patients gave written informed consent.

Received March 22, 2007; accepted April 12, 2007.
From the Department of Neurological Sciences (E.V., F.P., M.C.R., M.A., V.D.P., G.L.L.), and the Department of Vascular Surgery (M.F.G., B.G., F.B.V.), University of Rome “La Sapienza”, Italy.
Correspondence to Edoardo Vicenzini, Department of Neurological Sciences, University of Rome, “La Sapienza”, Viale dell’Università 30, 00185 Rome, Italy. E-mail edoardo.vicenzini@uniroma1.it © 2007 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.107.487918
Results
We enrolled 23 patients (mean age 69.6 ± 3.5; M/F 16/7). Two patients had light carotid stenosis (30%), 7 had moderate (40% to 55%) and 14 had severe carotid stenosis (65% to 90%).

Mainly during the diastolic cardiac phase, probably because of the reduced local pressure, the distribution of UCA inside the plaque allowed the visualization of vascularization. Microvessels were detected through the visualization of microbubbles penetrating in the iso-hyperechoic fibrous and fibro-fatty tissue, as a little vessel perpendicular to the carotid lumen, regardless the severity of stenosis. Furthermore, we constantly observed a small vessel under the ulceration. The diffusion of the contrast agent appeared to be in an “outside-in” direction, namely from the external intimal layers toward the inside of the plaque. Vascularization was not detected in the hyperechoic with acoustic shadow calcific tissue, nor in the hypoechoic necrotic and hemorrhagic areas (Figures 1 to 3; and supplemental movie clips 1 and 2, available online at http://stroke.ahajournals.org). The histological findings after endarterectomy in case 3 confirmed the presence of the microvessel within the plaque, corresponding to the image observed at the echo-contrast examination (Figure 4).

Discussion
Angiogenesis occurs regularly within atherosclerotic plaques and plaque vulnerability and symptomatic carotid disease have been associated with an increased number of microvessels. It is indeed believed that the absence of pericytes in new vessels causes the “leak” of potentially noxious and inflammatory plasma components into the extracellular matrix of the media/intima, increasing the plaque volume, gradually reducing vessel wall oxygen diffusion, enhancing further angiogenesis. In the final phase, the plaque is enveloped in luxurious adventitial vasa vasorum and intraplaque neovascularization, a hallmark of symptomatic atherosclerosis. For these reasons, plaque remodeling has been the target of medical therapies, such as statins, aiming at the possibility of transforming an unstable plaque into a more stable plaque, reducing the cerebrovascular risk.

In our patients, studied with ultrasound contrast pulse sequencing and SonoVue, we observed that UCA penetrates easily in the fibrous and fatty tissue and, according to our histological findings and to recent observations, it is related to the plaque vascularization. The constant observation of a little vessel under ulcerations may further support the hypothesis that intraplaque hemorrhage may be related to the rupture of newly formed intraplaque microvessels, a triggering factor for further embolic processes.

Contrast carotid ultrasound imaging appears then to be an emerging technique for clinical and research queries, quick to perform, easy to be repeated both at the bedside as well as in ambulatory patients, with low costs and invasiveness when compared with CT, MRI or positron emission tomography scans.

In asymptomatic patients addressed toward surgery, contrast carotid examinations could help to identify and quantify...
the presence and degree of plaque neovascularization, allowing a more reliable assessment of cerebrovascular risk.

Larger studies are also needed to clarify the prognostic value of plaque vascularization in those patients who are not candidates for surgery. UCA with ultrasound may be also applied in the evaluation of the effects of therapies aimed to plaque remodelling. As a matter of fact, we observed that plaque vascularization is present and detectable even in light to moderate stenosis and in asymptomatic patients not addressed to surgery.

Note: Video legend: clip 1 displays the contrast study of case 2; clip 2 the contrast study of case 3.

Disclosures

None.

References

Detection of Carotid Adventitial Vasa Vasorum and Plaque Vascularization With Ultrasound Cadence Contrast Pulse Sequencing Technique and Echo-Contrast Agent
Edoardo Vicenzini, Maria Fabrizia Giannoni, Francesco Puccinelli, Maria Chiara Ricciardi, Marta Altieri, Vittorio Di Piero, Bruno Gossetti, Fabrizio Benedetti Valentini and Gian Luigi Lenzi

Stroke. published online August 30, 2007;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2007/08/30/STROKEAHA.107.487918.citation

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2008/01/02/STROKEAHA.107.487918.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/