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Plaque angiogenesis identification with Contrast Enhanced Carotid Ultrasonography: Statement of the Consensus after the 16th ESNCH Meeting — Munich, 20-23 May 2011

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Summary Contrast Enhanced Carotid Ultrasonography (CCU) is capable of detecting angiogenesis within the carotid plaque as a potential index of plaque vulnerability. However, due to a lack of standard of examination technique and documentation, results are not sufficiently, reliably comparable.

To improve this situation and in order to support wide acceptance of this promising technique, experts in this field met in the Consensus conference in May 22, 2011, held during the 16th ESNCH Meeting (20—23 May 2011) in Munich, Germany, to discuss the limitations and problems and to determine guidelines for its proper use in scientific investigations and clinical practice.

The main results of this conference are presented here. The discussion is still in progress and individual conclusions may not reflect the opinion of all participants. It aims to provide a basis for a later comprehensive consensus statement.
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Introduction

The possibility that inflammation may represent an index of plaque vulnerability has brought the scientific interest to concentrate on the ''in vivo'' imaging the pathophysiological status of the atheroma, with the goal to identify the more vulnerable ones, to adopt the more adequate preventive strategies as early as possible.

Contrast Enhanced Carotid Ultrasonography (CCU) is nowadays a well-established tool for angiogenesis detection in several fields of application, with the principal advantage of ultrasound being a minimally invasive technique that allows ''real-time'' imaging. Since the first data of 2006, several papers have now described the possibility to identify adventitial vasa-vasorum and neovascularization in carotid plaques, with a specific pattern of vascularization in acute symptomatic lesions, and thus identifying ''plaque activity''.

Aim of this work is to describe the state of art of the methodology, to propose practical guidelines for CCU exam

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to obtain comparable data and to discuss the related clinical implications of plaque vascularization detection.

When to use

In moderate-to-severe internal carotid artery stenosis, both neurologically symptomatic and asymptomatic.

(a) Advantages in clinical routine:
- better Intima—Media-Thickness visualization;
- better plaque surface definition, especially in cases of large acoustic shadow calcified plaques;
- more sensible identification of plaque rupture and plaque ulcerations;
- improved sensibility in detecting carotid pseudoocclusion.

(b) Research objectives
- to identify vasa-vasorum and intra-plaque angiogenesis.

Suggested protocol and methods

CCU first requires the standard, basal exam of carotid plaques, to obtain the ''best view'' images, mandatory to be documented for further analysis. Ultrasound carotid duplex scanning should be performed with up-to-date ultrasound equipment, contrast enhanced ultrasound with machine-specific low-Mechanical-Index-software. The same, user defined ''machine presets'' have to be maintained constant in different examinations, to allow comparisons.

(a) Plaque basal assessment

Plaque echographic morphology has first to be recognized according to the criteria already established in literature. Plaque structure according to the echogenicity, as hyperechoic with acoustic shadow, hyperechoic, isoechoic, hypoechoic, and consequently as calcified, fibrous, fibro-calcified, fibro-fatty and hemorrhagic. Plaque surface as regular, irregular and ulcerated, when an excavation $\geq$2 mm in depth is observed. For easier data analysis in research studies, echogenicity might also be quantified with the Gray Scale Median (GSM) computerized analysis. The degree of stenosis should be evaluated according to North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria, as percentage of the difference between the distal diameter/area of the internal carotid artery and the residual lumen diameter/area at the maximum site of stenosis, and according to blood flow velocities.

(b) Contrast imaging

After having obtained the ''best view'' in basal imaging, contrast ultrasound exams can be performed using a linear transducer (9—4 MHz) with repeated short bolus injections in an antecubital vein (20 Gauge Venflon) of Sonovue (Bracco Altana Pharma, Konstanz, Germany), each bolus being promptly followed by a saline flush of 5 ml. Mechanical index should be kept as low as possible to allow vascularization identification. Real-time imaging — with high frequency transducers and high frame rates — should be used. Side to side imaging with B-mode could also be used to keep the ''best view'' on the screen. The exam should be digitally stored using clips of the real-time exam. These files can be transferred to an external PC for visual or computer-assisted off-line analysis. If possible, a clip of the whole contrast bolus administration should be obtained, to allow second ''crop'' of more significative findings. When computerized quantification is performed, similar epochs should be analyzed to compare findings from different patients, starting the analysis at the first appearance of the contrast agent in the carotid lumen. Clip length should not be inferior to 90 s each. The timer should be displayed on screen starting at the end of the contrast bolus injection.

Vascularization identification and quantification

After the bolus injection, few seconds are required for the contrast to be carried through the venous system to the pulmonary filter, heart and to the carotid arterial lumen. This time may differ from patient to patient, according to heart rate and ventricular ejection fraction. After the contrast is detected in the carotid axis, few seconds later, mainly during the diastolic cardiac phase, contrast agent may be shown inside the plaques allowing plaque vascularization detection. Microbubbles appear as little echogenic spots rapidly moving within the texture of the atheromatic lesion, easily identifiable in the real-time-motion, and depicting the small microvessels. The diffusion of the contrast agent appears to be in an ''outside-in'' direction, namely from the external adventitial layers toward the inside of the plaque and vessel lumen. Only in plaques in which the surface is fissurated or ulcerated the contrast agent show an ''inside-out'' direction, namely ''filling'' the void signal of the ulceration from the vessel lumen, thus better depicting the plaque surface rupture. In the ulcerated plaques small vessels are constantly observed under the ulceration. In recent atherothrombotic occlusion vascularization, expression of the highly active remodeling process, is usually observed. Vascularization is usually not detected in the hyperechoic plaque with calcific tissue acoustic shadow, nor in the hypoechoic necrotic and hemorrhagic areas of a plaque.

In acute symptomatic stroke patients due to carotid disease, a different pattern of vascularization may be observed: vascularization may be present as a major diffuse area of contrast enhancement at the base of the plaques, due to an agglomerate of many small microvessels, difficult to differentiate from each other, while the residual hypoechoic parts of the plaques, corresponding to the necrotic or hemorrhagic contents, usually remain avascularized. Furthermore, it has also been observed that the entity of the internal carotid stenosis may not be directly correlated with clinical symptoms: patients with smaller plaques, even without hemodyamic effect, may present plaque ''harmful'' characteristics and local areas of vascularization with intense ''plaque activity'', responsible for the distal embolization. If possible, all these features should be compared with the post-operative histology.

Contrast enhancement may be evaluated ''visually'' with qualitative scales, as well as ''semi-quantitatively'' using time-intensity curves. When visually evaluated, one must

always take into account the contrast distribution within the plaque texture (no bubbles detectable within the plaque, bubbles emanating from the adventitial side or shoulder of the plaque and moving toward the plaque core: clearly visible bubbles in the plaque) as well as by focal specific regions of contrast enhancement, usually observed even in smaller lesions and in acute symptomatic patients. Up to date, there is no consensus for time-intensity curves quantification method because: (1) region-of-interest is made only in a biplanar images; (2) the global whole plaque region selection may fail to reveal the small areas of high contrast enhancement; (3) the region-of-interest selection is highly operator dependent. Differently from the evaluation of the heart, in which myocardial tissue perfusion is the expression of a normal condition, and differently from small coronary plaques, in which there is a different ratio due to the size of the vessel, in carotid atherosclerosis this pattern may appear in only limited regions of the plaque and therefore quantitative analysis of the mean signal enhancement deriving from the whole plaque may not be expressive of the real perfusion. The finding of a ''harmful'' pattern of plaque vascularization may indeed be limited to a small area of the plaque, but its visual identification is, in our experience, highly representative of the ''plaque activity''. Some methods to obtain a ''ratio'' carotid lumen versus plaque texture has been proposed, with the same limitations related to the already described pitfalls in semiquantitative computerized analysis.

Conclusion and further implications

Contrast carotid ultrasound is an emerging technique, easily available and quick to perform, that adds important clinical and research information of the ''in vivo'' pathophysiological status, with low costs and invasiveness. In symptomatic stroke patients with carotid plaques addressed toward surgery, contrast carotid examinations could help to better analyze plaque morphology and to identify and quantify the presence and degree of neovascularization, allowing a further assessment of the cerebrovascular risk. Larger studies are though needed to clarify the prognostic value of plaque vascularization detection in asymptomatic patients with non-severe carotid stenosis that are not candidated for surgery. Moreover, the identification and evaluation of plaque angiogenesis may be in the future useful to evaluate the possible effects of therapies aimed to plaque remodeling.