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Contrast Enhanced Ultrasonography and Carotid Plaque Imaging: from the Hemodynamic Evaluation to the Detection of Neoangiogenesis - The New Approach to the Identification of the Unstable Plaque: from Morphology to Patophysiology

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1. Introduction

Ischemic Stroke (IS) represents the third leading cause of death in the Western World and it is particularly relevant because disability is a major frightening issue both for patients' quality of life, as well as for social and therapeutical implications (Engel, 1998).

One of the most frequent causes of Ischemic Strokes and Transient Ischemic Attacks (TIAs) is cerebral embolism that originates from atherosclerotic plaques in the carotid vessels. This "Large artery" (LA) pathogenesis accounts for 25-30% of all IS, i.e. more than 1/4 million per year, worldwide (Diener, 2004). In patients with a previous manifested TIA or IS, LA atherosclerosis is indeed observed in nearly 70% of the cases. Nonetheless, IS is proceeded by a TIA only in half of the patients with carotid atherosclerosis while, in the other half, Stroke may occur without the former manifestation of symptoms (Barnett, 1998).

In regards to preventive surgical strategies for carotid artery diseases, two major fundamental trials represent a "cornerstone" in treatment strategy of the carotid Strokes: these trials clearly and definitively confirmed the relationship between the risk of neurological events and the degree of the internal carotid artery stenosis. According to data collected from European Carotid Surgery Trial (Rothwell, 2004; ECST, 1991; ECST, 1998) and to the North American Symptomatic Carotid Endarterectomy Trial (Barnett, 1998) Stroke risk is correlated to the presence of hemodynamic internal carotid artery stenosis and occurrence of recent cerebrovascular symptoms. A general consensus has been reached on indications for Carotid Endoarterectomy (CEA), that at present has to be performed in

experienced centers in patients with: a) symptomatic severe stenosis (=/>70%); b) symptomatic stenosis (*with soft unstable plaque*) > 50%; c) asymptomatic patients with 70-99% stenosis below 75 years of age (Rothwell, 2004, Goldstein 2010, Hobson 2008, Liapis 2009).
On the other hand, the real benefit of CEA in asymptomatic patients, even though affected by severe hemodynamic degree of stenosis is still nowadays controversial and not clearly defined, as demonstrated by ACAS (ACAS, 1995) and ACST (Halliday, 2004) trials: only carotid stenosis > 70% would benefit from CEA, but only after five years follow-up and only in center where CEA is performed with very low perioperative complication rates (Halliday 2010, Kakkos 2009, Setacci 2009). When stenoses are below this threshold, patients are adressed towards medical therapy, which offers at present good results (Rothwell, 2004; CAPRIE, 1996, Goldberg 2010). Therefore the problem of primary prevention strategy exists for a high number of asymptomatic patients, that may transform into 250.000 new IS per year: in these patients, the surgical approach decided only on the severe degree of internal carotid stenosis may be no more valid.
It is mandatory to ameliorate the balance between risksa nd benefit of CEA in asymptomatic patients: during the last 30 years several potential risk factors have been evaluated to appropriately select subgroups of asymptomatic patients that may really benefit from CEA, but, however, without reaching satisfactory results and clear indications (Abbott, 2007; Nicolaides, 1995). At present, the recent ACES Study performed in asymptomatic patient with severe degree internal carotid artery stenosis (>70%) in order to detect risk factors significantly related with the onset of neurological events concluded that only the microembolism identified at 2 hours Transcranial Doppler monitoring is a true and independent predictor of cerebrovascular events., significantly linked with cerebral ischemia (Markus, 2010). For all the these reasons further studies are mandatory in order to select subgroup populations that really benefit of surgical treatment.
New evaluation methods have to be considered: the detection of the unstable, vulnerable plaques will have to use functional investigations methods, and no longer the morphological investigation alone is sufficient. Advances in carotid plaque imaging could allow functional investigations methods and the detection of vulnerable plaques has to be performed according to these new viewpoints. Due to all the above-mentioned controversial points, the risk-benefit and cost-effectiveness of CEA in asymptomatic patients have to be better characterized, identifying the real subpopulations that would really take advantages from a surgical preventive strategy, in favor of a safe secure benefit and long-term outcome.
In addition, being Stroke an unforeseeable event that occurs in a wide percentage of cases because of carotid embolic lesions, plaque morphology characterization has represented a fundamental step for the selection of patients at risk of cerebrovascular ischemic events. Nonetheless, in recent years, even all information about degree of stenosis and plaque morphology is not yet considered enough to recognize lesions at risk. New further concepts regarding functional activities of carotid plaques represent the future target to be investigated, in order to indentify the so called "vulnerable plaques" and, consequently, to avoid the disabling ischemic event.

1.1 The symptomatic plaque from the histological point of view

Histopathological data collected from carotid specimen of symptomatic patients have clearly identified the different morphological characteristics of the symptomatic plaques (Mauriello, 2010; Fisher, 2005) linked with cerebral ischemia and with the underlying mechanisms of plaque instability.

Beyond the degree of stenosis, the presence of plaques heterogeneity, large areas of intraplaque hemorrhage or a necrotic lipidic core, the presence of surface ulcerations, represent all peculiar characteristics of symptomatic, complicated carotid plaques. All histological studies have then confirmed that the underlying plaque morphology is an important further predictor of stroke risk (Gronholdt, 2001; Stary, 1995). Several studies have shown that plaque morphology have also to be considered an additional independent predictor of cerebral infarction and that carotid plaques at risk for rupture are not always correlated with the severity of stenosis at bifurcation sites. Other morphological characteristics seem to play a more relevant role (Griffin, 2010).

Several histopathological studies have compared the morphological aspects of carotid plaques removed from symptomatic and asymptomatic patients in attempt to better understand the mechanisms underlying plaque destabilization demonstrated that plaque rupture, thin fibrous cap and thrombogenic plaques with relevant inflammatory infiltration and increase of macrophage cells are main features of symptomatic plaques, prone to be responsible of embolic cerebrovascular events (Spagnoli, 2004; Carr, 1996; Fisher, 2005)

1.2 Ultrasonography for plaque characterization

Characterization of plaque morphological aspects seemed an excellent method for risk stratification of neurological events. Over the past twenty years, high-resolution ultrasonography represented a reliable tool for plaque characteristics investigation in vivo and in real-time. Still nowadays Color Duplex Ultrasonography is a reliable, repeatable and noninvasive top-level and first choice investigation method in the evaluation of supraortic vessels.

Historically, in 1983 Reilly and coll. (Reilly, 1983) introduced the first characterization of plaque structure according to data obtained from ultrasound investigations: the concepts of "homogeneous" and "heterogeneous" were introduced in clinical practice to define plaques characteristics related to cerebrovascular risk. Irregular surface and ulcerations has also been identified as morphological features predictors of cerebrovascular events (Dixon, 1982).

In 1985 Johnson and Colleagues (Johnson, 1985) established three different criteria describing plaque composition, including calcified, dense (less hyperechogenic than calcified lesions) or soft plaques (isoechogenic in comparison with blood).

In 1988, Gray-Weale and coworkers (Gray-Weale, 1988) described four different plaque types and proposed a classification of morphological features according to ultrasound imaging: Type 1 (anechoic to echogenic fibrous cap; Type 2 (predominantly, but anechoic areas with echogenic, less than 25% of the plaque); Type 3 (mostly hyperechoic areas with anechoic, less than 25% of the plaque); Type 4 (echogenic and homogeneous plaque).

In 1990, Widder (Widder, 1990) proposed a reverse classification, the most anechogenic plaques being assigned to Type IV and the most echogenic to Type I.

In 1993, Geroulakos (Gerulakos, 1993) introduced a modified version of Gray-Weale's classification including a 5th category of unclassified plaque reflecting calcified plaques which may have zones of acoustic shadowing which obscure the deeper part of the arterial wall as well as the vessel lumen.

Only in the following years the relative risk of plaque related to morphological characteristics according to a numerical quantification was the subject of a consensus meeting (De Bray, 1996) on the characterization of plaques: it was finally decided that the echogenicity of the plaque should have be standardized against 3 reference structures: blood flowing to anechoic, sternocleidomastoid muscle for isoechogenic, next to the transverse

processes of cervical vertebrae for hyperechogenicity Further studies suggested the use of the bright far wall of media-adventitia interface as a reference for hyperechogenicity (Joakimsen, 1997). After these early works many further studies have reported data regarding the successful correlation between the plaque morphology on ultrasound investigation and the histological plaque composition.

To further reduce the possibility of biases due to the subjective evaluation, computerized methods also have been introduced to evaluate echogenicity of carotid plaques. The standardized quantitative computerized assessment of plaque echogenicity by Gray Scale Median (GSM) represents nowadays an objective tool for the definition of the unstable plaques (El-Barghouty, 1995; Biasi, 1999). Data collected from literature have indeed clearly demonstrated that low GSM plaque values identify those lesions that are closely related to the prediction of the risk for embolic events (Biasi, 1999; Mathiesen, 2001).
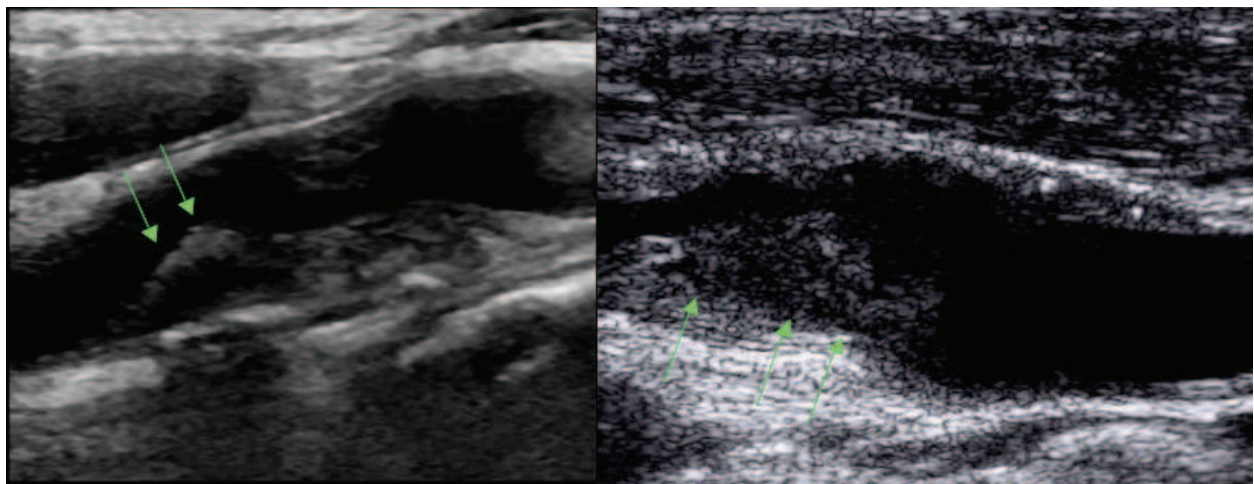

Fig. B-Mode imaging of soft plaques with a clear anechoic part in the distal posterior part of the plaque (green arrows, left) and with a superimposed iso-hypoechoic trhombus (green arrows, right).

1.3 From morphology to patophysiology

There is a general agreement that the identification of carotid artery vulnerable lesions is not possible nowadays only relying on the degree of stenosis and plaque morphological characteristics alone. Even if these features represent the conventional methods used for planning adequate treatment strategies, these methods are not capable of evaluating in vivo inflammation and remodeling of unstable plaques, and consequently to predict the true risk of cerebrovascular events. Surface rupture and luminal thrombus formation related to plaque acute inflammation are nowadays considered the major events related to the development of acute stroke.

Techniques aimed at imaging the biological "functional" status of the plaque are now emerging. Conventional radiological imaging such as Computerized Tomography Angiography with contrast agents (CT), Magnetic Resonance Imaging (MRI) and even Positron Emission Tomography (PET) have been recently applied to image targets of the biological functional pathways of carotid plaques. Nonetheless, up-to-date there is no "in vivo" imaging technique considered as the "gold standard" for the demonstration of the direct temporal correlation between inflammation and morphological features of carotid vulnerable plaques responsible of neurological events (Warburton, 2006). Moreover, being

not widely available and being expensive and radiation risk techniques, these tools cannot be used in the current ordinary follow-up. Despite the excellent results obtained on the validation and accuracy of ultrasonography, the true mechanism able to convert an asymptomatic plaque to a symptomatic one failed to be clearly identified and even if Duplex evaluation represented a further step in the knowledge, it seemed inadequate. Preoperative ultrasound carotid imaging can be used to detect the histological characteristics of plaque with the possibility of post-operative validation. Since recent clinicopathological studies have indicated the role of intraplaque hemorrhage and ulceration in symptomatic carotid disease, identification of these features is of high value in choosing therapy, especially for the asymptomatic patient.

From clinical studies a new concept has emerged: plaque 'vulnerability' i.e. the inner stability and risk for rupture other than morphology and degree of stenosis may be more adequate (Reilly, 1983; Hennerici 2004). Thus, a functional diagnostic test (instead of a pure anatomical imaging) would be preferable as current clinical anatomical investigations have a poor ability to predict which plaques become symptomatic in the immediate future.

2. Plaque angiogenesis

The clinical complications of atherosclerosis are caused by local thrombus formation, which results from the rupture and fissuration of surface of an unstable atherosclerotic plaque. The formation of microvessels (angiogenesis) in an atherosclerotic plaque contributes to the development of plaques, increasing the risk of plaque rupture.

Only recently has the in vivo evaluation of angiogenesis received attention for its possible role in assessing the vulnerability of the atheroma. The presence of microvessels in atherosclerotic plaques was firstly described by Paterson in 1936-38 and Geiringer (1951) as well as their lack in the non atherosclerotic - normal, non pathological - arterial wall: these were simply pure observational studies, very far to connect with a patophysiological mechanism. From histological reports it is well known that angiogenesis is linked with the vulnerable, unstable plaque characteristics. Moreover, although the detailed pathophysiological mechanisms of plaque formation and rupture are still under debate, there seems to be reasonable evidence that smooth muscle cell hypertrophy, proliferation and migration through the basal membrane, macrophage infiltration, LDL deposition and intimal neoangiogenesis are crucial steps finally leading to plaque vulnerability and rupture. Histological studies have indeed shown that microvessels are not usually present in the normal human intimal layers and that intima becomes vascularized only with the development of the atherosclerotic process and when its layer grows in thickness (Geiringer, 1951).

Only in the last 20 years the presence of the adventitial vasa vasorum and the occurrence of plaque neovascularization was recognized and identified as a significant marker of plaque instability and confirmed in histological studies, as predictors of unstable atheromasic lesions in cerebro and cardiovascular patients (McCarthy, 1999; Mofidi, 2001).

3. Ultrasound contrast agents for functional plaque imaging

In the last few years, Contrast Enhanced Ultrasonography (CEUS) performed with 2nd generation contrast agents and new dedicated software represent a useful tool that improved not only the diagnostic accuracy of ultrasonography, but allowed the detection of

vascularization and tissue perfusion in real-time and with excellent spatial resolution in many fields.

CEUS is a safety (Piscaglia 2006, Abdelmoneim 2009), emerging tool that allows to obtain more reliable information in daily practice (Claudon, 2008). As a matter of fact, regarding the evaluation of carotid atherosclerosis, CEUS provides an enhanced assessment of the arterial lumen and plaque morphology, an improved resolution of carotid intima-media thickness, and they even allow the direct visualization of adventitial vasa vasorum and plaque neovascularization (Purushothman, 2006; Feinstein, 2004). Feinstein et al reported in 2006 first experiences identifying carotid plaque neovascularization with CEUS in a patient with a significant and symptomatic carotid stenosis, confirmed by the histological findings after endarterectomy. They also observed the neovascularization regression after 8 months of statins therapy in a plaque of a diabetic patient. In a recent paper from our group (Vicenzini, 2007), we also observed that plaque vascularization can be easily detected with contrast ultrasound imaging in the the fibrous and fibro-fatty tissue and not observed in the calcific nor in the necrotic and haemorrhagic areas, as expression of plaque remodeling. More evidences are now confirming the reliability of this technique (Shah, 2007; Huang, 2008, Staub, 2010; Coll 2010).

In our research, we focus on the possibility to detect neoangiogenesis in carotid plaques with ultrasound and second-generation ultrasound contrast agents. In order to detect possible differences between atherosclerotic lesions correlated with clinical symptomatology, we studied patients to be submitted to carotid endarterectomy for severe, hemodynamic internal carotid artery stenosis, both asymptomatic as well as acute/recent symptomatic cerebrovascular patients. Data obtained were also confronted with post-operative histological findings. Moreover, asymptomatic patients with moderate internal carotid artery stenosis suitable for medical treatment and sonographic surveillance were investigated. Aim of our study was to evaluate the characteristics of carotid plaque vascularization detected with contrast ultrasound investigation according clinical findings, and to correlate contrast ultrasound investigation with histology and immunohisto-chemichal (VEGF, MMP3,CD 31-34).

3.1 Methods of CEUS investigation

Carotid duplex scanning was performed with an Acuson/Siemens Sequoia 512 and Siemens S2000 scanners, equipped with the software "Cadence Contrast Pulse Sequencing technology" (Cadence CPS). Linear phased array probes (6, 8 and 15 Mhz for the Sequoia, 9, 14, 18 MHz for the S2000). General Electric (GE Logiq9) and Philips IUD 22 scanner were also used. The same presets were maintained for all patients, in order to reduce pitfalls reproducibility.

Internal carotid artery plaques were digitally documented in B-Mode, Color and Power modes on both longitudinal and transversal scans, to obtain the best visualization of the atherosclerotic lesions. Angle corrected blood flow velocities were obtained with Pulsed Wave Doppler at the maximum site of stenosis. Plaque echographic morphology has been described according to criteria already well-established in literature (Gray-Weale, 1988; El Bargouthy, 1995): plaque structure according to the echogenicity, and considered as hyperechoic with acoustic shadow, hyperechoic, isoechoic, hypoechoic, and consequently as calcific, fibrous, fibro-calcific, fibro-fatty/haemorrhagic. Plaque surface as regular, irregular and ulcerated, when a surface irregularity > 2 mm was detected. Echogenicity was also quantified with Gray Scale Median (GSM) computerized analysis (Biasi, 1999) in order to

better define the plaque risk. The degree of stenosis was evaluated according to European Carotid Surgery Trial criteria (ECST, 1995), as percentage of the difference between the original and the residual lumen at the maximum site of stenosis and to the relative increase of blood flow velocities (Sabeti, 2004).

Contrast ultrasound investigation was performed, as already described (Vicenzini, 2007), after small repeated bolus injections of SonoVue (Bracco Altana Pharma, Konstanz, Germany) in an antecubital vein (20 Gauge Venflon), followed by saline flushes. After identifying the plaque on longitudinal and transverse scans, and after having obtained the baseline B-mode, Color and Power images of the plaque, the 15 Mhz linear array probe with a mechanical index varying from 0.4 to 1.4 with CPS continuous real-time recording software was used to achieve the best visualization of plaque morphology and vascularization, in the same longitudinal view. Freezed images and clips were stored throughout the investigation, in order to compare the basal images with the same images obtained after contrast administration. The "Contrast Agent only" software feature, in which the image is derived only from the signals originating from the microbubbles, has been used. All the investigations were digitally stored onto an external hard-disk for the off-line review analysis, performed by two different sonographers.

Carotid endarterectomies have been carefully performed in order to obtain the whole plaque with minimal trauma. The removed plaques were immediately placed in formalin and subsequently probed with hematossilin-eosin coloration, to have a general view of plaque cellularity, and immunostained with antibodies for Vascular Endotelial Growth Factors (VEGF) and Matrix MetalloProteinases 3 (MMP3) (DAKO, Glostrup Denmark). After the complete observation of the lesion, the regions of interest observed at ultrasound images were identified and discussed with the sonographers.

4. Contrast ultrasound findings

Ultrasound contrast agent microbubbles are visualized few seconds after the injection as a hyperechoic dynamic flow in the carotid vessel lumen, providing an enhanced visualization of the carotid intima-media complex and a better identification of the plaque surface. They may be of help in better defining plaque surface and to indentify plaque ulceration, especially when B-Mode imaging and Color imaging are blurry or have a low definition.

Mainly during the diastolic cardiac phase, probably due to the reduced local pressure, the distribution of UCA inside the plaque allowed the visualization of vascularization. Microvesseles 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.

Further, a different pattern of plaque vascularization was observed in the acute symptomatic patients, represented by a major and more diffuse contrast enhancement, completely different from the pattern of the majority of the asymptomatic plaques. These data have been confirmed by other Authors (Xiong, 2009; Staub, 2010, Chowdhury ,2010, Cosgrove, 2009).

Histological specimens with immunostaining obtained from CEA confirmed a relevant angiogenesis in symptomatic plaques when compared to asymptomatic ones. From our experience (Vicenzini, 2007, 2009; Giannoni, 2009 a, 2009 b), we observed that microbubbles diffuse easily in the fibrous tissue of carotid plaques and that histologically correspond to the newly generated vessels, so confirming that plaques angiogenesis could be related to
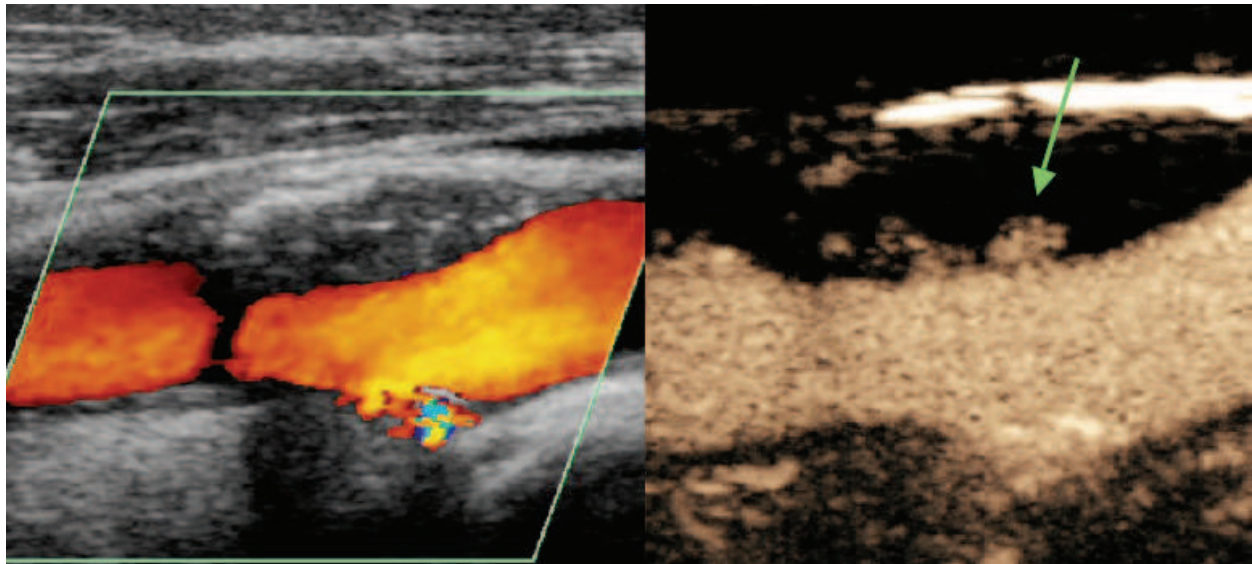
Fig. 1. Contrast carotid ultrasound of a ulcerated plaque. Ultrasound contrast agents better identify plaque surface and ulceration (green arrow).
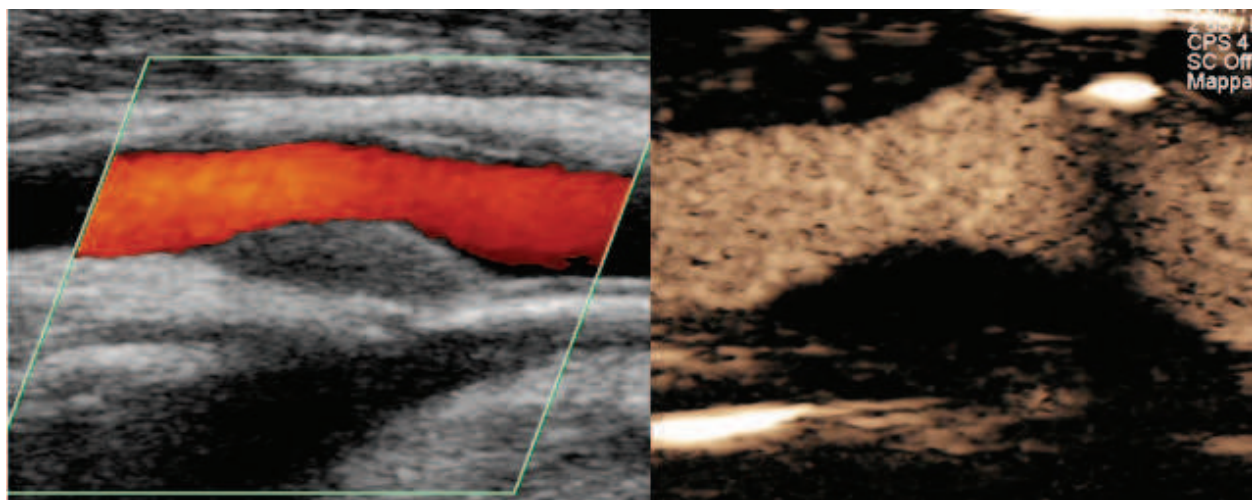

Fig. Isoechoic, fibrous plaque with regular surface determining moderate internal carotid artery stenosis in an asymptomatic patient. No vascularization observed at contrast ultrasound.

progression and remodeling. In these regards, several Authors reported the strong histological correlation between the density of the new vessels in the intima and the incidence of luminal stenosis, the extent of chronic inflammatory infiltrates, the evidence of granulation tissue, thus confirming that symptomatic coronary and carotid artery plaques are characterized by a high vascularized pattern (McCarthy, 1999; Mofidi, 2001; Fleiner, 2004; Spagnoli, 2004; Dunmore, 2007).

The relevance of angiogenesis in atherosclerosis is driving efforts to develop accurate and reliable imaging modalities able to quantify plaque neovessels in-vivo. The ideal non-invasive technique should have a high resolution and be widely available and reproducible. In cardiology, angiogenesis and microvessels observed in coronary atheromas in histological studies have proven to be strongly associated with unstable angina and myocardial infarction. These observations lead then to the concept that the coronary atherosclerotic

plaque, when in a late phase of development, becomes richly vascularized, unstable and responsible of the coronary artery occlusion and/or distal embolization, with consequent myocardial ischemic damage (Fryer, 1987; El Barghouty, 1995; Mofidi, 2001; Spagnoli, 2004). Morevoer, in our experience, contrast ultrasound shows vasa-vasorum and plaque newly-formed microvessels with an outward-inward direction, probably witnessing the patophysiological mechanism responsible of intraplaque microvessels rupture resulting in plaque increase of volume and surface rupture, trombotically active. The immunohistochemical sampling confirmed the relevant neoangiogenesis in these areas. On the other hand, the vascularization pattern was quite different in asymptomatic plaques, that showed less contrast enhancement with histological demonstration of more mature microvessels of higher caliber, rarely distributed in the plaque context. These contrast ultrasonographic findings are confirming histological data showing that every plaque has its own vascularization and that neoangiogensis is relevant in the unstable and symptomatic carotid plaque, as in the coronary arteries (Barger, 1984). New vessels formed within an atherosclerotic lesion have to be considered a "locus minoris resistentiae", because they are particularly prone to rupture, thus causing intra-plaque haemorrhage, increased plaque volume and instability. Several factors have been identified as contributors to the neovascular response of the atherosclerotic plaque: hypoxia and ischemia occurs when the intima and media undergoes thickening, inducing the production of angiogenic factors such as vascular endothelial grow-factor (VEGF), in particular in the diabetic patient (Williamson 1993). With the rupture of these microvessels, intraplaque haemorrhage stimulates the inflammatory response of macrophages and T cells to produce angiogenic factors, further promoting angiogenesis and increase of plaque volume.
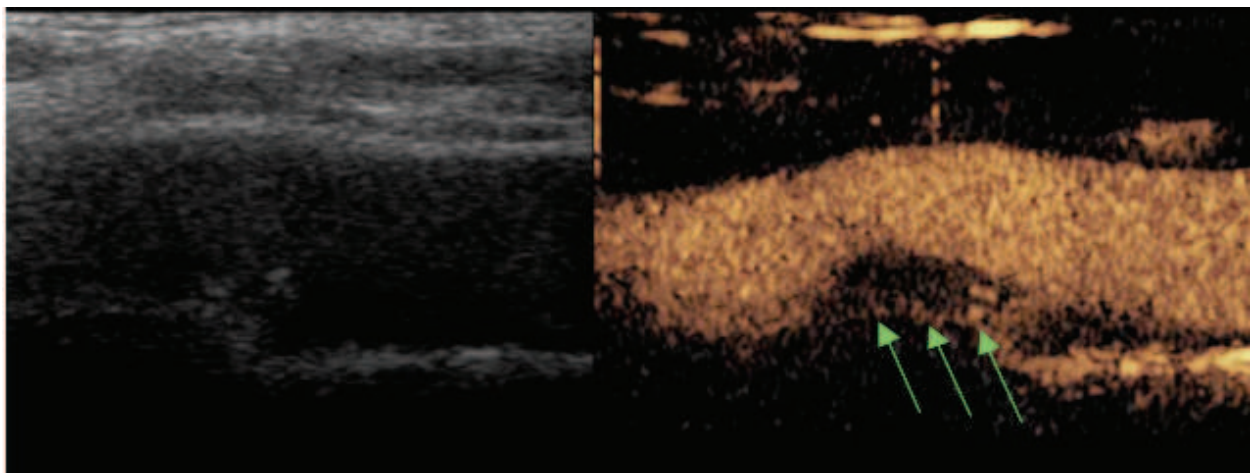

Fig. Acute symptomatic vascularized plaque. Green arrows show microbubbles in the plaque texture.

5. Role of inflammation and intraplaque angiogenesis

The patophysiological mechanisms responsible for progression and change towards carotid plaque instability remain incompletely defined. Consequently, there is an important need to identify if other elements play a key role in the progression and embolism from carotid plaques. Nowadays, the importance of inflammation and inflammatory markers has been claimed as a fundamental factor involved in the development and progression of the

atherosclerotic plaques; furthermore, the association between inflammation, atherosclerosis progression and cardiovascular events have been well established for coronary and carotid artery diseases (Libby, 2002; Ridker, 2003, Monaco 2009, Monaco 2010, Shalhoub 2009, Shalhoub 2010.). Histological studies have observed that stable plaques are indeed characterized by a chronic inflammatory infiltrate, whereas vulnerable and ruptured plaques are characterized by an active inflammation and "plaque activity" processes involved in the thinning of the fibrous cap, predisposing to plaque rupture (de Nooijer, 1996; Spagnoli, 2004; Spagnoli, 2007). Nonetheless, the occurrence of high plaque neovascularization originating from the external layers and the increased number of adventitial vasa-vasorum have been considered, and confirmed in histological studies, as other important predictors of unstable achromatic lesions in symptomatic and asymptomatic carotid artery plaques (Mofidi, 2001; Dunmore, 2007), through different mechanisms that may be connected with plaque inflammation. Angiogenesis occurs indeed regularly within atherosclerotic plaques and plaque vulnerability and symptomatic carotid disease have been associated with an increased number of microvessels (Fleiner, 2004). 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 adventitial vasa vasorum and rich network of small caliber microvessels, a hallmark of symptomatic atherosclerosis (Carlier, 2005). The processes that lead to intramural haemorrhage and plaque ulcerations are other important issues that have been extensively studied. Some theories claims the hypothesis that atherosclerosis progression is due to an "outside-in" process and, effectively, intimal vessels originating from the adventitial layers have been observed much more frequently that those originating from the luminal side, resembling microvessels that grow within tumors (Kumamoto, 1995; Mofidi, 2001; Dunmore, 2007). This datum was also confirmed in our patients, in which the microbubbles diffusion seems to be oriented from the external adventitial layers towards the internal intimal lumen and, constantly, through a little vessel present under the plaque ulcerations.
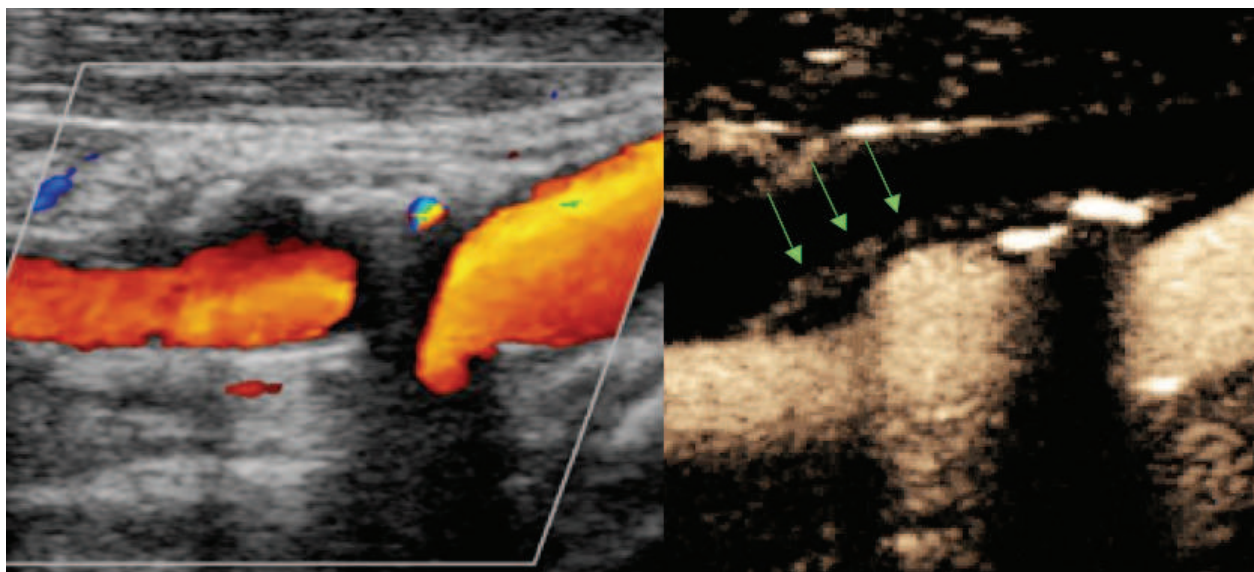

Fig. Plaque vascularization in the area below ulcerations

This latter observation further supports the theory that intraplaque hemorrhage and ulcerations can be related to the rupture of newly formed intraplaque microvessels, that, being immature and with a thin wall, are submitted to local triggering factors such as mechanical forces and shear stress. The histological observation that intraplaque hemorrhages are common in every atherosclerotic lesion, usually deep and not connected with the vessel lumen, is another indicator that the bleeding originates locally (Bornstein, 1990; Milei, 1998).

6. What is new and good, what is not good

The most relevant information that can be obtained with CEUS is that plaque angiogenesis is possible to be demonstrated in vivo and in "real time". A limitation of this approach is the modality of the evaluation of these patterns of vascularization: at present, a method of a real numerical objective quantification is indeed not available for carotid plaques. Differently from the evaluation of myocardium, in which 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, this pattern may interest limited regions of the carotid plaque and the quantitative analysis of the mean signal enhancement deriving from the whole plaque cannot be easily applicable. The semi-quantitative evaluation, being arbitrary, may not be considered as really representative of plaque vascularization, also because evaluated in bi-dimensional images on user-defined region of interest. The identification of these patterns requires then a very careful visual and morphological observation. Moreover, at present, conventional CEUS imaging is provided through a bidimensional plane, that is not able to give complete information regarding the whole plaque angiogenesis, also considering that plaques can be either or not vascularized with avascular areas, due to necrosis, hemorrhage or calcifications.

7. Future research

Standard ultrasound carotid duplex is one of the most diffuse and available technique to assess plaque morphology and to identify the "plaque at risk". With Ultrasound Contrast Agents, more information on carotid atherosclerosis can be identified in routine clinical practice: as a matter of fact, an enhanced assessment of the arterial lumen and plaque morphology and an improved resolution of carotid intima-media thickness can be obtained. Consistent data also report that the direct visualization of adventitial vasa vasorum and plaque neovascularization is now possible with this technique, with the main advantage of being simple, low cost, minimally invasive and "in vivo". These data could open future perspectives to study unstable carotid plaques with contrast ultrasound to evaluate plaque progression and the possible efficacy of medical therapies. In these regards, the efficacy of statins in cardiovascular prevention has been established (Mizuguchi, 2008). Several papers suggested that the pleiotrophic effects of statins may contribute to plaque stabilization reducing inflammation (Yamagami 2008; Kadoglou, 2008) and, potentially, all these features could be evaluated with contrast ultrasound. The innovative aspect of this study is that data obtained from histological specimens are detectable "in vivo", with minimal invasiveness, by contrast ultrasound investigation.

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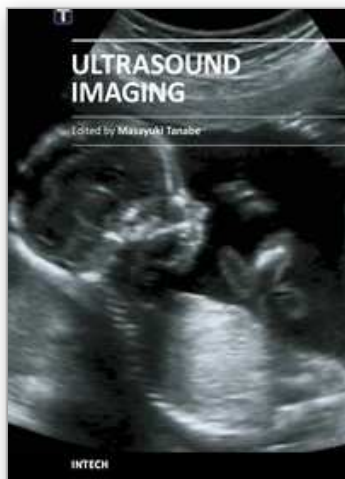
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