Review Article on Advanced Imaging in The Diagnosis of Cardiovascular Diseases

# Carotid plaque imaging profiling in subjects with risk factors (diabetes and hypertension)

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**Abstract:** Carotid artery stenosis (CAS) due to the presence of atherosclerotic plaque (AP) is a frequent medical condition and a known risk factor for stroke, and it is also known from literature that several risk factors promote the AP development, in particular aging, smoke, male sex, hypertension, hyperlipidemia, smoke, diabetes type 1 and 2, and genetic factors. The study of carotid atherosclerosis is continuously evolving: even if the strategies of treatment still depends mainly on the degree of stenosis (DoS) determined by the plaque, in the last years the attention has moved to the study of the plaque components in order to identify the so called "vulnerable" plaque: features like the fibrous cap status and thickness, the volume of the lipid-rich necrotic core and the presence of intraplaque hemorrhage (IPH) are risk factors for plaque rupture, that can be studied with modern imaging techniques. The aim of this review is to give a general overview of the principle histological and imaging features of the subcomponent of carotid AP (CAP), focalizing in particular on the features of CAP of patients affected by hypertension and diabetes (in particular type 2 diabetes mellitus).

**Keywords:** Carotid artery plaque; diabetes; hypertension

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## Introduction

Carotid artery stenosis (CAS), due to the presence of atherosclerotic plaque (AP) is a frequent medical condition and a known risk factor for stroke (1); in fact, it has been estimated that 15% of ischemic strokes are caused by large vessel atherosclerosis (1-3). It is also known from literature that several risk factors promote the AP development, in particular aging, smoke, male sex, hypertension, hyperlipidemia, smoke, diabetes type 1 and 2, and genetic factors (4-7).

Several guidelines have been introduced for the treatment of symptomatic CAS (SCAS) and asymptomatic CAS (ACAS) (8). According to the recent guidelines of the European Society of Vascular surgery (ESC) and European Society of for Cardiovascular Surgery (ESCV) the degree of CAS is still considered the main feature to take into consideration for the management of CAS (9).

However, this paradigm is changing, mainly thanks to the technological innovation of the last 10 years: the study of carotid artery atherosclerosis is moving from the mere evaluation of the degree of stenosis (DoS) to the plaque composition in order to identify the "vulnerable plaque" (3,10); for example, a patient with low-grade stenosis and ulcerated CAP would benefit more from a revascularization procedure than one with a stable CAP with a thick fibrous

cap (FC) that determines a high-grade stenosis (11). The recognition of these features is often challenging, but it can be helpful for improving the management of these patients.

This aim of this paper is to give a general overview on the main imaging features of Carotid AP (CAP) in subjects with diabetes and hypertension, focusing in particular on the pathogenetic mechanisms, histological features of CAPs, and on the imaging features of the single plaque subcomponents.

## Pathogenesis and histological features of carotid artery plaque

The pathogenesis underlying plaque development is still matter of study and debate. Recent published papers suggest that the key pathogenetic mechanism is represented by a self-perpetuating propagating complex inflammatory process involving the arterial wall, called as positive feedback hypothesis (12). According to this hypothesis, low density lipoproteins (LDL) play a central role in this process. LDLs can move from the blood circulation to the arterial wall through endothelial cells by using specific scavenger receptors (12,13) sensitive to estrogen levels (12,14). The remodeling process of the arterial wall starts when LDLs accumulate beneath the intimal layer forming a lipidic core. The remodeling process of the arterial wall can be positive or negative (10,15,16): positive remodeling is characterized by dilation of the vessel wall following the increase CAP volume, with little or absent compromise of the vessel caliber, while negative remodeling is characterized by the reduction of the vessel lumen. LDLs tend to spontaneously oxidize (ox-LDL) because of their molecular instability, and ox-LDLs act as pro-inflammatory molecules and stimulate the recruitment of circulating monocytes from circulating blood (12). Once inside the plaque, macrophages themselves contribute to the inflammatory and growth process of the plaque phagocytizing ox-LDLs and becoming foam cells (17); further, the production of ox-LDLs and other proinflammatory molecules stimulates neoangiogenesis, proliferation of the intimal smooth muscle cells, and endothelial dysfunction (12). This inflammatory environment inside of the plaque promote the production of other ox-LDLs in a self-feeding process that determines the necrosis of the lipidic core, forming the so-called lipid-rich necrotic core (LRNC) (12,18), and the remodeling of the extracellular matrix with the production of a FC on the luminal surface (19). Inflammatory cells tend to accumulate mainly in the shoulder regions and near to the FC of CAP (3,20). The neovessels generated by the inflammatory response inside the AP are usually immature and fragile (21) and tend to break and to determine to intraplaque hemorrhage (IPH) (22). Necrotic debris, apoptotic cells, and extracellular matrix can act as nidus for development of calcifications (23); further, osteoblastic-like cells and multinucleated giant cells, that result morphologically similar to osteoclasts, are frequently found in CAP, especially in regions of calcification and fibrosis (23). Some examples of the above-mentioned histological components of CAP are reported in *Figure 1*.

The erosion or rupture of the FC can determine the exposition of the necrotic core components to the blood flow, with release of embolic particles able to reach the distal brain vessels, and with activation of the coagulation cascade and formation of a superimposed thrombus that compromise the arterial lumen (18); the clinical manifestation of this process is the ischemic syndrome (18).

According to the pathological process above described, APs can be classified in six different types by using the well-validated criterion of the American Heart Association (AHA) (11,24) (*Table 1*): type I AP is characterized by isolated deposition of macrophages foam cells in the arterial wall, type II AP are fatty streak lesions characterized by intracellular lipidic deposits, whereas in type III AP the deposition of lipids is also extracellular (11,24). Type IV lesions are known also as "atheroma" and they are clinically relevant: this type of AP is characterized by the presence of a dense lipidic core that consists of macrophages and inflammatory cells and no FC or surface defects are present (11,24). On the other hand, type V AP is characterized by the presence of FC and of neoangiogenesis inside the lepidic core: this type of plaque can three different subtypes: Va characterized by the presence of a lipid core; Vb characterized by the presence of a partially calcified lipidic core; Vc with a lipid-poor core (11,24). Type VI AP are characterized by fissured FC with hemorrhage and thrombotic deposits (11,24). A similar system was introduced by Cai *et al.* for classifying APs on magnetic resonance (MR) imaging (32).

The composition of the plaque can differ also in relation to different factors, included the common risk factors for atherosclerosis such as diabetes and hypertension. A pathological study by Spagnoli *et al.* (33) in fact evidenced that CAP of patients with hypertension are characterized by the presence of numerous mononuclear cells, whereas the CAP of patients with hypercholesterolemia are rich in foam and mononuclear cells and are covered by a thinner

 

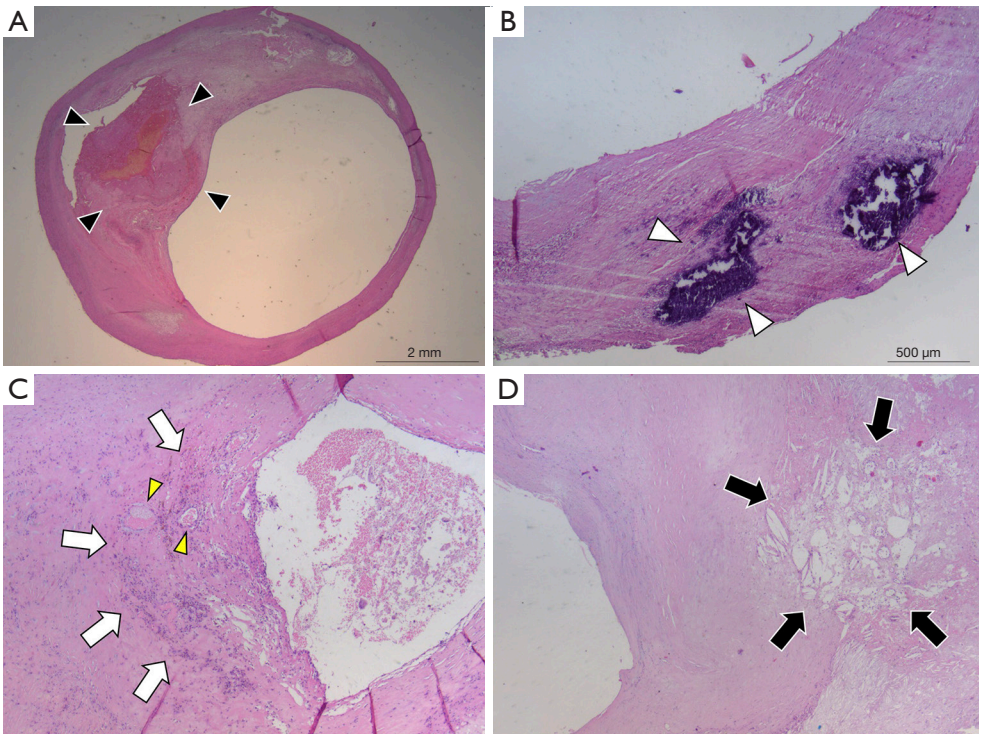


**Figure 1** Features of the vulnerable plaque in different CAPs samples, examined with hematoxylin-eosin. (A) IPH (black arrowheads) is clearly visible in the context of the CAP. (B) Calcifications inside the plaque (white arrowheads). (C) Two small vessels derived from neoangiogenesis (yellow arrowheads) are visible in the context of intraplaque inflammation. (D) LRNC foci (black arrows). CAP, carotid atherosclerotic plaque; IPH, intraplaque hemorrhage; LRNC, lipid rich necrotic core.

**Table 1** Principle markers of plaque vulnerability

| |
|---|
| Carotid artery stenosis degree (8,9) |
| CAP volume (10,25,26) |
| Thin or fissured FC (3,27,28) |
| Presence of LRNC (3,27,29) |
| Inflammation and neoangiogenesis (30) |
| IPH (22,31) |

CAP, carotid artery plaque; FC, fibrous cap; LRNC, lipid rich necrotic core; IPH, intraplaque hemorrhage.

FC; in contrast, the CAP of patients with smoking habit is associated with few mononuclear and giant cells, bigger quantities of connective tissue and greater incidence of thrombosis and calcifications. Lastly, CAP of patients with diabetes (both type 1 and 2) are characterized by the presence of large amount of connective tissue, presence of numerous giant cells and few foam cells (33), and a recent research by Yahagi *et al.* (34) evidenced that AP of patients with diabetes generally exhibit larger necrotic core and more inflammatory cells when compared to those of non-diabetic patients.

Statins demonstrated to be effective in stabilization of CAP (35); however, their effects on APs are still not well understood (36), even if it is known that higher levels of statins reduce plaque volume sustained not by reduction of necrotic core but mainly by increase of dense calcium volume (37).

## Imaging features of carotid artery plaque subcomponents

The stenosis of the carotid artery, as well as the status of the carotid arterial wall, the volume of the CAP and its subcomponents can be analyzed *in vivo* by different noninvasive imaging modalities, included ultrasound (US), contrast enhanced US (CEUS), computed tomography (CT) and Dual Energy Computed Tomography (DECT), MR and nuclear medicine, in particular $^{18}$F-fluorodeoxyglucose

 

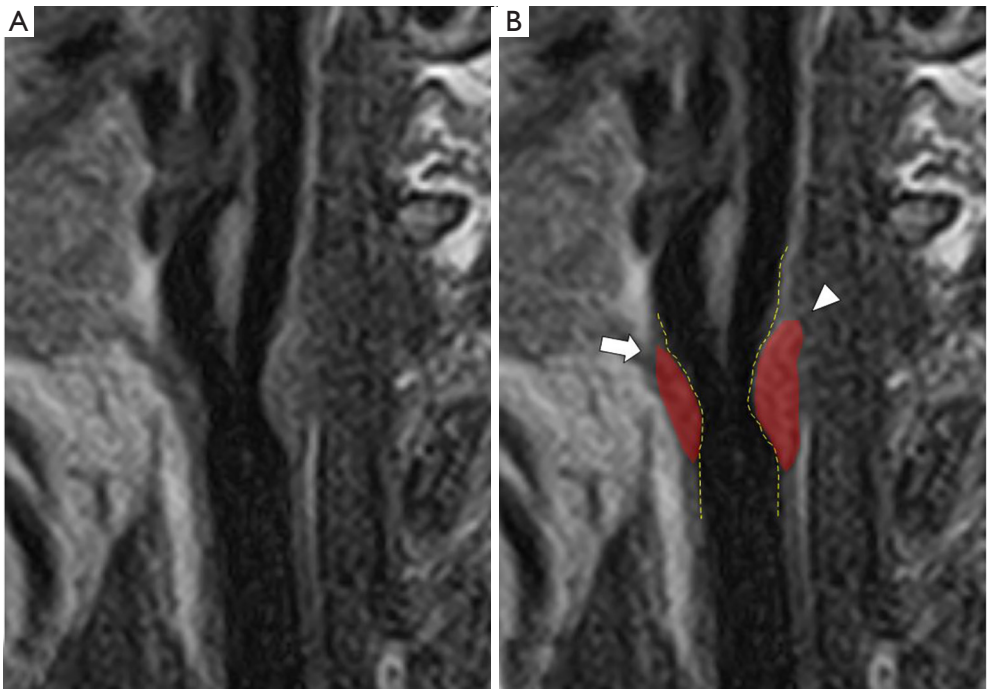


**Figure 2** Left carotid artery of a 56 years old man with clinical history of type 2 diabetes mellitus analyzed with a 3 Tesla MR scanner. (A) T1-weighted sequence of the carotid artery bifurcation; the plaque appears slightly hyperintense on T1 sequences as for high lepidic component. (B) Detail of A: the lumen (yellow dashed lines) is restricted by the plaque (red areas); the upper portion of the plaque is extended in the external carotid artery (white arrow) and partly in the internal carotid artery (white arrow head). MR, magnetic resonance.

positron emission tomography ($^{18}$FDG-PET) combined with CT or MR (38). Their characterization is fundamental in order to assess the vulnerability of CAP (3), underlying that the main components that make a CAP "vulnerable" are: (I) presence of thin or fissured FC, (II) presence of LRNC and calcifications, and (III) presence of inflammation and IPH (3,10,22). In the following paragraph we will analyze the features of these subcomponents, in particular those to be taken into account for accurate evaluation of plaque's risk of rupture in patients with risk factors for atherosclerosis. A list of the principle markers of plaque vulnerability is reported on *Table 1*.

We invite the readers to refer to the Expert Consensus Recommendations of the Vessell Wall Imaging Group of the American Society of Neuroradiology (ASNR) (10) for the imaging protocols of study of CAP.

### *Quantitative measurements of lumen and carotid artery plaque volume*

One of the best known and widely studied parameters of risk of stroke is represented by CAS degree (8,9); for example, in order to reduce the risk of stroke, carotid revascularization through endarterectomy or stenting placement is indicated for patients with a recent (<6 months) history of stroke/transient ischemic attach (TIA) and CAS degree between 70–99% estimated using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method (9,39). Smoking habit (40), diabetes (6) and hyperlipidemia (41) are all independent risk factors associated to internal CAS due to the presence of CAP.

CAS degree can be widely studied by US, CT and MR (3) (*Figure 2*): the best method is represented by MR because of its contrast resolution and excellent reproducibility, that makes it optimal for cross-sectional and longitudinal studies. CT is faster than MR, but the presence of calcifications can lead to overestimation of wall areas (3). US is widely available, accurate and reproducible for plaque and stenosis measurements, but it is observer dependent and calcifications can lead to acoustic shadowing (3).

As well as the lumen stenosis, the increase of CAP volume predicts cardiovascular events (10,25,26), and some authors suggested that this parameter can be also a better parameter that could indicate the severity of atherosclerotic

 

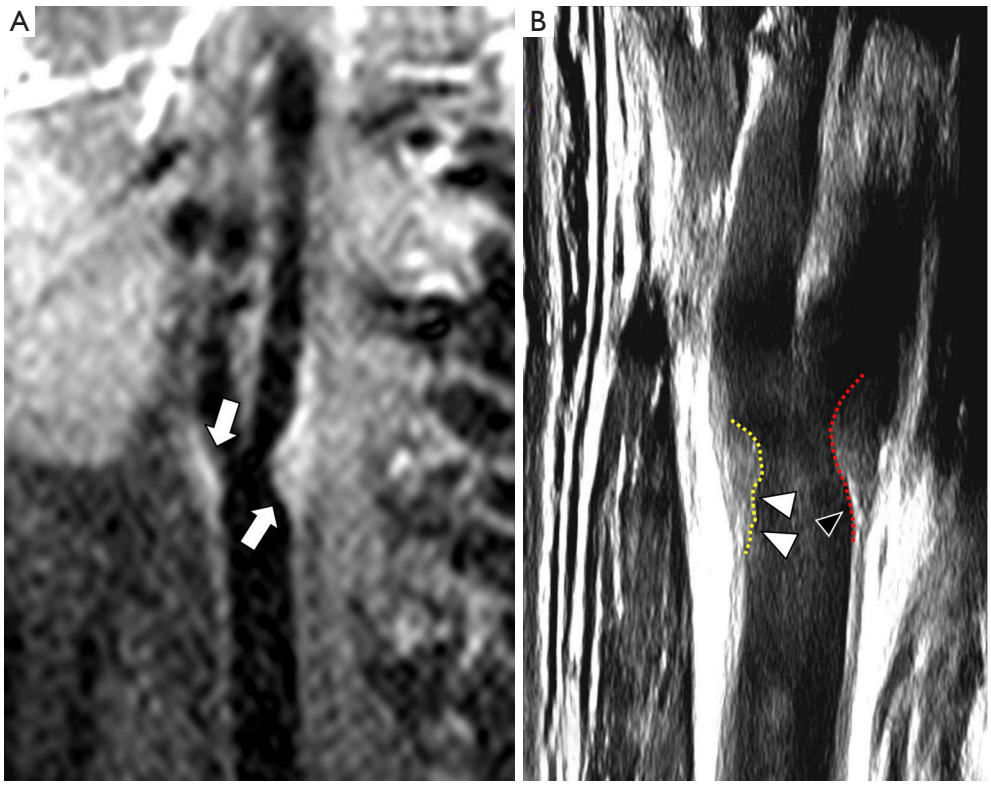


**Figure 3** The same patient of *Figure 1* was studied on a 3 Tesla MR with a T1-weighted fat-suppressed sequence and with US. (A) The plaque is clearly visible and it results slightly inhomogeneously hyperintense when compared to the adjacent tissues on T1-weighted fat-suppressed sequence due to the high-lipid component. (B) The US of the same vessel evidence that the border of the plaque adjacent to the internal carotid artery (red dashed line) is regular and with a the FC hyperechoic in the lower part as for the presence of calcifications (black arrowhead); the portion of the cap next to the external carotid artery (yellow dashed line) is irregular as for the presence of small defects <1 mm. US, ultrasound; FC, fibrous cap.

disease (42). Recently, a study by Lu *et al.* (43) evidenced that the progression of the CAP volume is associated with an increased risk of occurrence of cerebrovascular events). Beside CAP volume, CAP composition is another parameter to be taken into consideration: CAP composition has a crucial row in plaque's stability (3,10). In the next paragraphs will be discussed the principle features of CAP, but it is interesting to note for example that the ratio IPH/lipid volume is associated with cerebrovascular events as demonstrated by a recent study by Saba *et al.* (44). CT and MR are able to calculate the volume of the plaque: CT can identify and quantify calcified component, whereas accurate and reliable quantification of both IPH and LRNC is not possible; on the other hand, MR is the best technique for assessing IPH and LRNC (3,10). However, the use of dedicated algorithms can overcome the limitations of these techniques identifying and precisely quantifying plaque tissue characteristics on imaging: for example, a recent research by Sheahan *et al.* (45) evidenced that software algorithms are able to mitigate the beam hardening and blurring artifacts of routine CT angiography giving accurate quantification of CAP components with high correlation between imaging analysis and *ex vivo* histological data.

### *Fibrous cap thickness, surface morphology and lipid rich necrotic core*

FC thickness, surface morphology and the lipidic content of CAP are strongly associated with systemic cardiovascular outcomes (3,46): unstable CAPs in fact are characterized by the presence of a thin FC and a large necrotic core (27), and the presence of ulcerations is considered a risk factor for stroke (3,47). Among the risk factors, it is remarkable to underline that diabetes.

 

FC thickness has a pivotal role in CAP stability (3,10). It is remarkable to underline for example that type 2 diabetes is associated with thinning of the FC (48). Even if there is not unique consent about the distinction between "thin" from "thick" FC, a FC thickness <200 μm is considered as reference value for identifying "thin" FC (49-51). The other parameter to be taken into account in the evaluation of CAP is the FC status in terms of surface morphology; this can be smooth, irregular (presence of small irregularities ranging from 0.3 to 0.9 mm) or ulcerated (presence of cavities 1 mm depth) (*Figure 3*) (3). An intact FC is associated to low-risk plaque rupture, whereas the risk of rupture is mild for thin FC and high for fissured FC, and the best technique for assessing FC is MR (28). Intact FC is often not usually well detectable on proton density (PD), T1 and T2 sequences (52), but on time-of-flight (TOF) sequence it commonly appears as a hypointense juxtaluminal band: in case of thin FC this band could be absent, whereas in case of fissured FC the absence of juxta-luminal band is associated with the presence of plaque hemorrhage and/or mural thrombus that appears as a mild hyperintense area next to the lumen (28,49-53). The use of T1-weighted sequence after gadolinium-based contrast medium injection can be used to improve tissue characterization between the FC and the underlying lipidic core (54,55). FC thickness evaluation is feasible also with other technique, even if with suboptimal results; for example, on US it appears as a hyperechoic juxtaluminal structure on contact with the hypoechoic circulating blood (27). Even if US is often able to distinguish between thin and thick FC (56), it is important to remember that this methodology is operator dependent and that even modern US scanners have a spatial resolution between 200–600 μm (47); similarly, the low spatial resolution of modern CT scanners (0.5–0.625 mm) is not optimal for the study of FC (56), and FC cannot be differentiated from soft plaque component (3). On the other hand, CT angiography is considered excellent for the evaluation of the surface morphology and superior to MR because of its superior spatial resolution, whereas US is not considered the technique of choice even if the use of US contrast medium and the application of 3D methods can improve ulceration detection (3).

LRNC is a predictive parameter of increased risk of stroke (3,29). It is known in fact that LRNC size is predictor of FC disruption (10,57), in particular when LRNC area exceeds 40% of vessel wall area (26). As exposed above, LRNC is constituted by cholesterol crystals, debris and calcium deposits in variable percentages (3,11,33). Both CT and MR are able to identify the LRNC (3). LRNC can be easily detected on MR imaging as a focal hypointense area on T2-weighted sequences (10,58,59), and as a focal non-enhancing region within the carotid vessel wall on post-contrast T1-weighted images (10,55,60). CT is superior to MR in detection of calcium components (3), but it is not able to distinguish LRNC from IPH because these two entities show attenuation values <60 Hounsfield units (3,61). US is not useful for differentiating the main plaque components, and in particular it is not able to differentiate between IPH and LRNC (3).

### *Inflammation and neovascularization*

As seen above, the presence of inflammation in the atherogenic process promotes the angiogenetic process (20), and it is considered a marker of plaque vulnerability (30). In the last years several researches were conducted to evaluate the utility of $^{18}$FDG-PET in combination with CT (62,63) or MR (64) for the study of CAP inflammation but, even if it is considered the best imaging method for accurate detection of CAP inflammation, there is still no consensus on cut-off of $^{18}$FDG uptake for identifying and quantifying it (3,65). MR studies on *ex vivo* carotid samples using iron nanoparticles (i.e., ultrasmall superparamagnetic irox oxide or P947) that can be incorporated by phagocytic cells within the CAP determining loss of signal on T2* sequences, have shown promising results for the evaluation of inflammation (10,66,67). However, inflammatory process and neoangiogenesis can be indirectly evidenced also by using dynamic contrast enhanced MR (DCE-MR): in fact the study by Kerwin *et al.* (68) found an association between the plaque enhancement measured by DCE-MR and inflammation, and in particular the transfer contrast ($K^{trans}$) resulted to be correlated with the histologic markers of inflammation (presence of macrophages, neovasculature and loose matrix); further elevated $K^{trans}$ values were found in smokers patients when compared to non-smokers. Another study by Kerwin *et al.* (69) purposed average $K^{TRANS}$ within the adventitia as quantitative measurement related to the extent of vasa vasorum. According to these findings, to the study by Millon *et al.* (70) and the considerations by Wasserman (71), it is possible to affirm that gadolinium enhancement of CAP is related to inflammatory process and vulnerable plaque phenotype.

Contrast enhanced US (CEUS) allows researchers to detect intraplaque vascularization thanks to its high spatial and temporal resolution (72,73). The plaque enhancement

 

on CEUS can be subjectively classified in three grades according to the regions of the CAP in which microbubbles spread: (I) mild, when microbubbles can be seen in outer parts of CAP; (II) moderate, when microbubbles are visible both inside the CAP and in its shoulder regions, and (III) severe, when microbubbles can be observed in all the plaque regions, including the apex (74). However, further studies are needed in order to normalize and standardize the CEUS technique for clinical practice (73), even if it is remarkable to underline that CEUS has been already used in experimental studies in order to monitor the response to statins treatment, as seen for example in the study by Tian *et al.* (75) that found that atorvastatin significantly inhibits the development of adventitial vasa vasorum.

It has been demonstrated also on CT that contrast enhancement of CAP is correlated with neoangiogenesis (*Figure 4*) (3,10): for example, a correlation between contrast enhancement of the CAP and microvessels density in CT was found by Saba *et al.* (76), and a more recent study by Romero *et al.* (77) evidenced that the enhancement of CAP reflecting neoangiogenesis is strongly associated with acute neurological symptoms in patients with internal CAS between 50–70% assessed by NASCET (39).

### *IPH*

IPH is another mark of CAP vulnerability (22,31). IPH can occur because the neovascularization promoted by the inflammatory process is characterized by the presence of immature and not-well structured microvessels (22,78). Neovessels are more fragile and easier to break in response to the physiological blood pressure, blood flow and wall shear stress when compared to the normal microvessels (79-81).

IPH appears echolucent on US, and it is quite similar to the aspect of the LRNC (22,81,82). As we have seen in the previous paragraph, CEUS is able to detect intraplaque vascularization, even if the technique is still not standardized in clinical practice (73), but to the best of our knowledge up to date no studies have demonstrated the capability of this technique to identify IPH (22). The identification of IPH on CT angiography is still debated (83), but a recent research by Saba *et al.* (84) suggested that a HU threshold <25 after contrast medium injection is indicative of the presence of IPH. However, up to now, MR is the technique of choice for evaluating IPH (22): in fact, with this imaging technique IPH can be detected with a sensitivity between 82–97% and a specificity between 74–100% (28). However, the age of IPH influence its appearance on MR because of the different oxidative status of the iron inside the hemoglobin (85): IPH usually appears hyperintense on T1-weighted and TOF sequences and variable signal on T2-weighted and PD sequences (22). T1-weighted fast spin-echo (T1-FSE), T1-weighted sampling perfection with application-optimized contrasts using different flip angle evolution (T1-SPACE) and T1-weighted Magnetization Preapred Rpid AAcquisition Gradient Echo (T1-MPRAGE) are the sequences that show the higher sensitivity and specificity for the detection of IPH (86), whereas other sequences such as the multicontrast atherosclerosis characterization (MATCH) sequence (87) and the simultaneous non-contrast angiography and IPH (SNAP) sequence (88) have shown promising results for IPH evaluation.

## Features of vulnerability in high risk subjects

Several risk factors often coexist at the same time in patients with CAT interacting and influencing one to each other, and for this reason it is difficult to study the specific effects of every single risk factor (89-92). However, in the last years some papers have been authored demonstrating that some categories of patients, accepted as high risk, have peculiar features in their carotid artery plaques, and it is possible that advanced algorithm would make easier to detect and characterize the single effect of these risk factors in the future (93). There are several categories that can be considered at high risks, but in the following section we will focus our attention to the hypertension and type 2 diabetes mellitus (T2DM).

### *Hypertension*

Hypertension is considered one of the strongest biomarker associated with the occurrence of cerebrovascular events as demonstrated in a recently published paper by Flint *et al.* (94): researchers analysed data derived from a population of 1.3 million adults, and they found that both systolic and diastolic hypertension influence the risk of adverse cardiovascular events included myocardial infarction, ischemic stroke and hemorrhagic stroke, regardless the threshold used for the definition of hypertension (blood pressure values ≥140/90 mmHg or ≥130/80 mmHg).

How does this reflect in CAP composition? To the best of our knowledge, not many studies have investigated this aspect, taking into account the fact that more than a

 

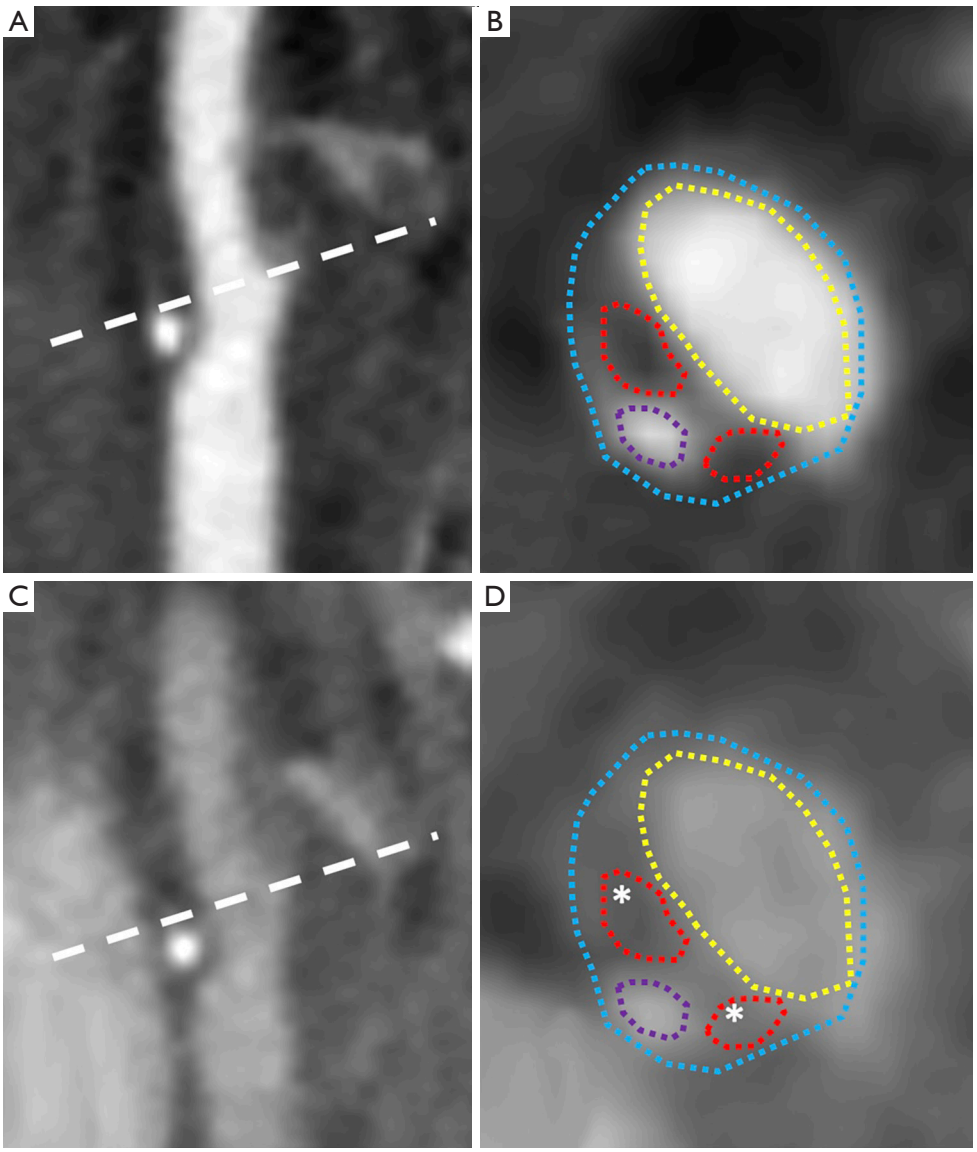


**Figure 4** Examination of an eccentric atherosclerotic plaque of the bifurcation of the right carotid artery of a male patient with clinical history of hypertension. (A) Sagittal and (B) axial view of the plaque on CT angiography scan; (C) sagittal and (D) axial view of the plaque on delayed post-contrast phases. The white dashed lines in (A) and (C) represent the axial section of the vessel visualized on (B) and (D) respectively. In (B) and (D) the lumen (yellow dashed line) is restricted due to the presence of a crescent-shaped AP identified between the lumen and the adventitia (blue dashed line); inside the plaques we can identify a calcification (purple dashed line) and two areas of neovascularization (red lines); note in (D) how these two areas of neovascularization appear more hyperdense in delayed scan when compared to the angiographic scan (white asterisks). CT, computed tomography

single risk factors are often present at the same time in a patient; however, we can make some considerations. As previously seen, Spagnoli *et al.* (33) evidenced that the presence of numerous mononuclear cells characterized the CAP of hypertensive patients. A recent study by Fassaert *et al.* (95) analyzed 1,684 underwent to carotid endarterectomy, and they found that patients with pre-operative hypertension (defined as systolic blood pressure ≥160 mmHg) a statistically significant association between systolic hypertension and presence of calcifications,

 

**Table 2** Main features of plaque vulnerability in patients with hypertension

| |
|---|
| Presence of numerous mononuclear cells (33) |
| Association between increased systolic blood pressure and presence of calcifications, macrophages, lipid core >10% of plaque area, microvessels and IPH (95) |
| Association between increased diastolic blood pressure and presence of macrophages, lipid core and IPH (96) |
| Increased wall volume (96) |
| Progression of CAP above the bifurcation (97) |

IPH, intraplaque hemorrhage; CAP, carotid artery plaque.

**Table 3** Main features of plaque vulnerability in patients with T2DM

| Main features of plaque vulnerability in patients with T2DM |
|---|
| Presence of numerous inflammatory cells (in particular giant cells), fewer foam cells, larger amount of connective tissue and larger necrotic core when compared to those of non-diabetic patients (33,34) |
| T2DM is associated to the development of vulnerable plaque irrespectively of the degree of carotid stenosis (101) |
| More intraplaque calcium components and increased expression of genes related to inflammation (102) |
| Increased plaque burden and negative remodeling compared with healthy controls (103) |

T2DM, type 2 diabetes mellitus.

macrophages, lipid core >10% of plaque area, microvessels and IPH, and increased diastolic blood pressure with macrophages, lipid core and IPH, and all these features are typical of the vulnerable CAP. It is also know that hypertension is associated with increased wall volume as reported by Chien *et al.* (96); in the same article, it is also interesting to underline that patients in therapy with angiotensin converting enzyme inhibitors (a category of drugs commonly used for the treatment of hypertension) is associated with increased thickness of the FC of CAP. Lastly, it is important to underline that hypertension influences also the progression of CAP: a recent study by Lu *et al.* (97) that analyzed the annual segment-specific progression of CAP by using serial contrast enhanced MR evidenced that hypertension and smoke are risk factors for the progression of CAP located above the bifurcation but not for those located below the bifurcation. The main features of. plaque vulnerability above mentioned are resumed in *Table 2*.

### *T2DM*

Simirarly to hypertension, the diabetes status is considered a features of increased risk in terms of cardvioascular mortality as shown by Rawshani *et al.* (98), and it is also known that the prevalence of atherosclerosis and CAP is higher in patients with T2DM (99). A study by He *et al.* (100) for example evidenced a relatively high prevalence of non-calcified and non-obstructive CAP in a cohort of 195 patients with T2DM that suffered of TIA or stroke.

The specific effects of T2DM on carotid remodeling and CAP composition remains elusive even if some researches focused on this topic. T2DM acts independently on the atherosclerotic process and it has been demonstrated by Esposito *et al.* (101) that T2DM is associated to the development of vulnerable plaque irrespectively of the degree of carotid stenosis. T2DM in particular influences CAP composition, acting on inflammation and on the deposition of calcium (34). As previously seen, CAP of patients with diabetes are characterized by the presence of numerous inflammatory cells (in particular giant cells), fewer foam cells, larger amount of connective tissue and larger necrotic core when compared to those of non-diabetic patients (33,34); another recent study by Menegazzo *et al.* (102) confirmed these data analyzing carotid endarterectomy specimens from 59 patients and finding that although the plaque composition of and the degree of calcifications were similar between diabetic and non-diabetic patients, there were statistically significant differences in terms of plaque calcium component and expression of genes related to inflammation. It is reasonable considering that these features can be also observed on imaging, but to the best of our knowledge only one clinical

 

research by Laugesen *et al.* (103) analysed the progression of CAP in diabetic patients on MR imaging: the authors compared 100 patients with T2DM (duration <5 years) and 100 healthy controls, finding that patients with T2DM showed increased plaque burden and negative remodeling compared with healthy controls. The main features of plaque vulnerability above mentioned are resumed in *Table 3*.

Lastly, it is important to remember that CAP is predictive of underlying silent coronary atherosclerosis prevalence and severity in patients with T2DM (104) and that for this reason some authors suggest that carotid US might be a valuable prognostic tool for this category of patients (105), even if the occurrence of CAP can be underestimated by using US when compared to CTA as demonstrated by Ramanathan *et al.* (106).

## Conclusions

In the last years the evaluation of CAP by imaging has changed from the sole evaluation of the DoS to the evaluation of the plaque subcomponents in order to try to identify the "vulnerable" plaques. Some recent studies evidenced that risk factors for atherosclerosis such as diabetes and hypertension tend to modify CAP composition, that can be detected also by imaging, but further studies are needed to better understand their impact on the evolution of the atherosclerotic process and to optimize the treatment strategies.

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