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Neuroimaging of the Vulnerable Plaque

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Abstract: Plaque vulnerability due to inflammation has been shown to be a participating factor in the degenerative process in the arterial wall that contributes to stenosis and embolism. This is believed to have an important role to play also in the genesis of stroke or cerebrovascular diseases. In order to appropriately screen patients for treatment, there is an absolute need to directly or indirectly visualize both the normal carotid and the suspected plaque. This can be done with a variety of techniques ranging from ultrasound to computed tomography (CT) and magnetic resonance imaging (MRI). In addition to angiographic techniques, direct imaging of the plaque can be done either by ultrasound or by the so-called molecular imaging techniques, *i.e.* positron emission tomography (PET). These findings, together with other clinical and paraclinical parameters should finally guide the therapeutic choice.

Keywords: Plaque, arteriosclerosis, carotid artery, inflammation, magnetic resonance imaging, positron emission tomography.

INTRODUCTION

Stroke is a disease with an important socio-economic impact and which is caused often by the presence of an emboligenic plaque most often on the carotid bifurcation. In the absence of treatment it is associated with a high morbidity and mortality; this has prompted recent developments in both diagnosis and treatment of stroke [1]. Beyond that now lies the challenge of prevention, where detection and treatment of carotid disease is a major challenge [2]. Patients with 80% to 99% carotid stenosis lesions had a 20.6% annual event rate. When studying a series of patients with mild carotid artery disease, Rockman found that the main factor that appears to predict increased risk for future stroke is progression of stenosis [2]. A significant carotid stenosis can be found in approximatively one third of patients with cerebral ischemia. Overall carotid atherosclerosis is responsible for approximately 20% of all cerebral ischemic strokes. At 2 years of follow-up, the risk of a repeat stroke is 28 and 13 % for symptomatic stenoses of 70-99% and 50-69%. Carotid endarterectomy is now well established as a way to prevent infarction in the presence of carotid stenosis either symptomatic and of a higher grade than 50%, or symptomatic or asymptomatic of a higher grade than 70%. This was proven by two randomized clinical trials, the European Carotid Surgery Trial [3] and the North American Symptomatic Carotid Endarterectomy Trial [4]. The implications of these trials were that beyond surgery treatment of carotid stenosis should be undertaken. For asymptomatic stenosis the same recommendations have been made [5]. Carotid stenting is becoming an accepted alternative approach to carotid revascularization [6]. Stenting has become an established alternative treatment for coronary and peripheral vascular disease and has the advantage of avoiding general anaesthesia and neck incision, therefore being associated with lower mortality and morbidity rates. The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) found that endovascular treatment had similar major risks and effectiveness at prevention of stroke during 3 years compared with carotid surgery [7]. A recent randomized trial in 344 patients showed that among patients with severe carotid-artery stenosis and coexisting conditions, carotid stenting with the use of an emboli-protection device is not inferior to carotid endarterectomy [8]. Endovascular treatment with cerebral protection potentially has the advantage of avoiding minor complications however this has not been shown by recent studies and carotid endarterectomy (CEA) still remains the method of choice for treatment of stenosis [9]. The presence of an inflammatory process in the plaque itself is believed to contribute to the occurrence of embolic events. We review this phenomenon and the contribution of various imaging techniques in the evaluation of the inflamed carotid artery.

STROKE AND CEREBROVASCULAR DISEASES

Ischemic stroke is a leading cause of mortality and morbidity in industrialized countries. Stroke may be due to a multitude of factors and is divided into ischemic and hemorrhagic strokes. Ischemic stroke is mostly due to embolism that may be of cardiac or of vascular origin. One of the major causes of stroke is embolism from an existing carotid plaque. Traditionally, the carotid artery, and its pathology has been investigated by carotid angiography, at first standard and then digital subtraction angiography. With recent refine-

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ments in medical imaging technology, it has been possible to also non-invasively assess the carotid artery by Doppler ultrasound techniques as well as MR and CT angiographic techniques. While there is an agreement that the standard work-up in additional to the clinical assessment comprises ultrasound usually followed by MR angiography, there is sometimes a need to go further in the investigation of patients with suspected carotid artery disease. Also, the traditional indication for a treatment such as CEA or even stenting in selected cases is based on the presence of symptomatic disease, *i.e.* where there is not just the presence of a stenotic lesion but also a repercussion at the cerebral level that will be associated with a clinical deficit.

In the case where an ischemic event has occurred, it is necessary to additionally assess the status of the cerebral parenchyma. This will be possible since any kind of cerebrovascular evaluation we recommend will have included some kind of tissular imaging of the brain, be it with CT or MRI. In the event that one is faced with an acute event, this becomes a more complex treatment with two diseases having to be dealt with: on the one hand a stroke that may require thrombolysis and on the other hand the underlying stenosis that may require treatment as well.

CAROTID ARTERY DISEASE

Carotid disease associated with embolism is mostly due to arteriosclerosis which is a diffuse disease affecting the whole vasculature. The so-called vulnerable plaque may be an additional cause of embolism due to thrombus creation or rupture of the plaque itself. One of the possible processes that play a role in rendering a plaque vulnerable is the presence of an inflammatory process.

INFLAMMATION OF THE PLAQUE

A number of studies support the presence of an inflammatory process in the genesis of plaque vulnerability underlying embolism in arteriosclerosis. Both pathological studies ad genetic and immunological studies have shown alterations in parameters associated with plaque evolution.

MODERN NEUROIMAGING TECHNIQUES

The techniques that allow to image human vessels *in vivo* have evolved enormously over the last two decades. Indeed, we have gone from a situation where angiography was the standard examination to a situation where it is only proposed when an intervention is planned; this is in great part due to the massive development of much less invasive imaging modalities such as MR angiography, CT angiography and ultrasound techniques. From a conventional point of view, one is going to look for the presence of irregularities in carotid wall thickness, of the presence or absence of plaque erosions or even ulcerations.

ULTRASOUND

Due to its inherently non-invasive aspect, Doppler ultrasound is going to be the examination of choice in first line when investigating patients with carotid artery disease. Ultrasound allows the observer to assess vascular diameter and thus the presence or absence of stenosis and also permits non invasive determination of arterial flow. Additionally, in well-trained hands, Ultrasonography can also be used to investigate the morphology of the carotid wall as well as the morphology of the plaque [10].

Thus, using s scale of echogenicity it is partially possible to determine the risk of embolism in symptomatic and asymptomatic patients with Carotid stenosis [11].

COMPUTED TOMOGRAPHY

Computed tomography techniques have established themselves as being an important adjunct in the investigation of patients with cerebrovascular diseases [12]. First of all, its

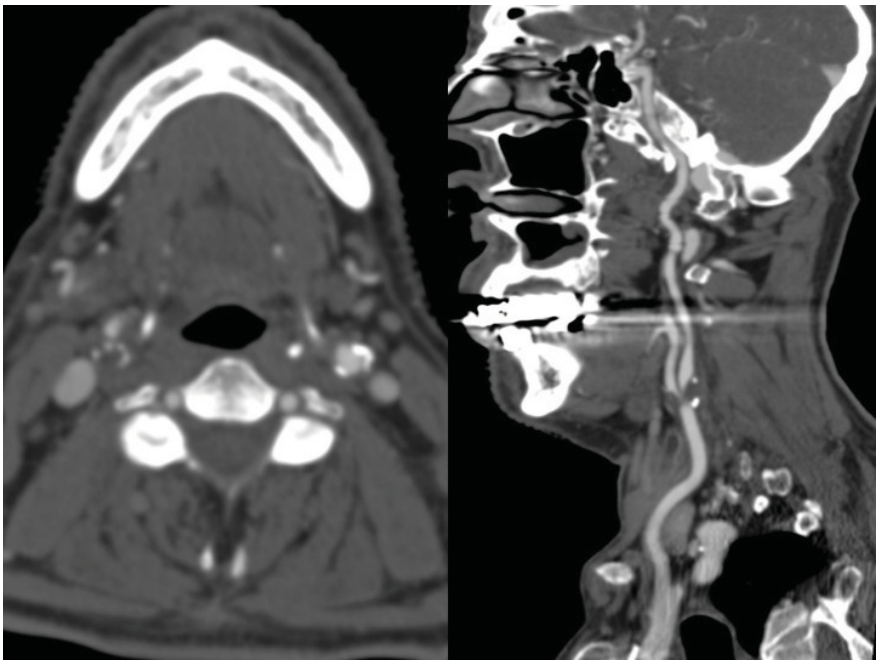
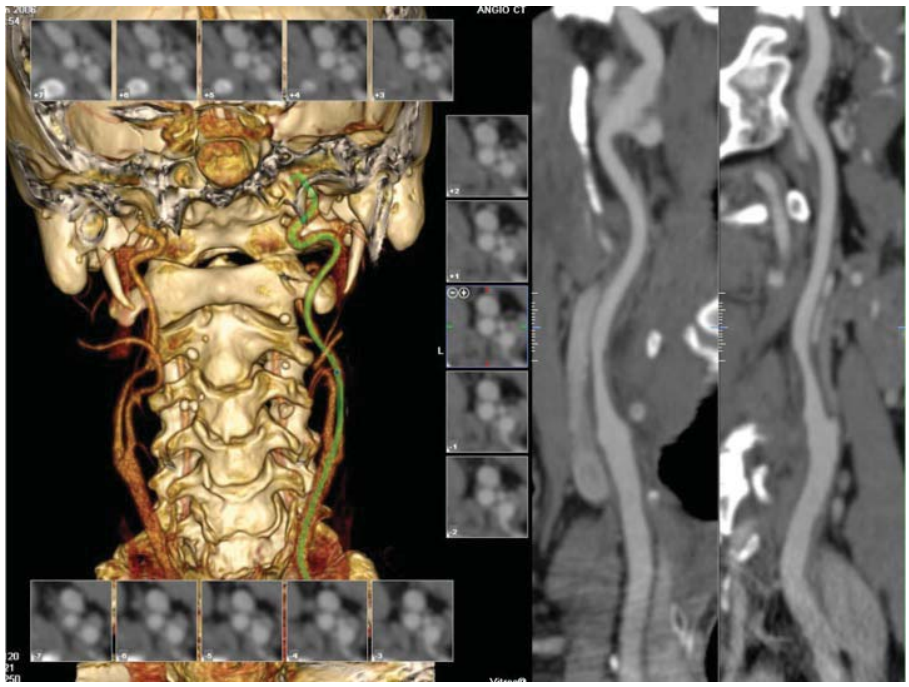


Fig. (1). Angio CT of the carotids in a patient with bilateral calcifications with a significant stenosis (lateral and axial views).



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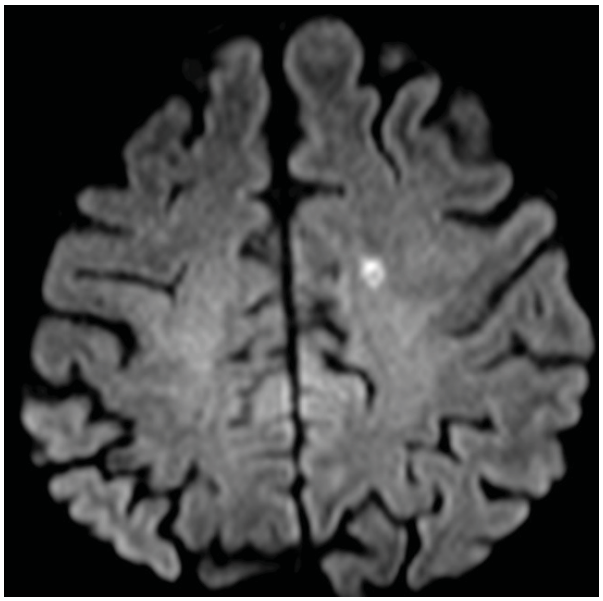


B

Fig. (2). CT and Angio-CT in a patient with carotid stenosis and stroke. Note the calcifications and irregularities in the vascular wall (**a**). There is an acute infarct on the DWI in the left centrum semi-ovale (**b**).

capacity to detect brain hemorrhage in unequalled, then its capacity to detect early changes such as brain edema is also very powerful and these two qualities make CT very the examination of choice at least for patients with a cute events. Additionally, and this has been an important evolution in the last two decades, CT angiographic techniques have evolved with the development of spiral CT scanning and multidetector arrays that allow to cover greater volumes in less time. While the use of an iodinated contrast agent probably contributes to provide with a luminographic effect that most resembles the one obtained with cerebral angiography, additionally, CT is able to most well demonstrate the presence of calcific plaques. Examples of CT images are provided in (Figs. **1-3**).

MAGNETIC RESONANCE IMAGING AND ANGIOGRAPHY (MRI & MRA)

Magnetic Resonance Imaging, due to its non-radiating nature and its inherent sensitivity to motion and thus flow, should be the natural candidate for imaging of the arteries. While this was in theory true from the beginning, MR imag-

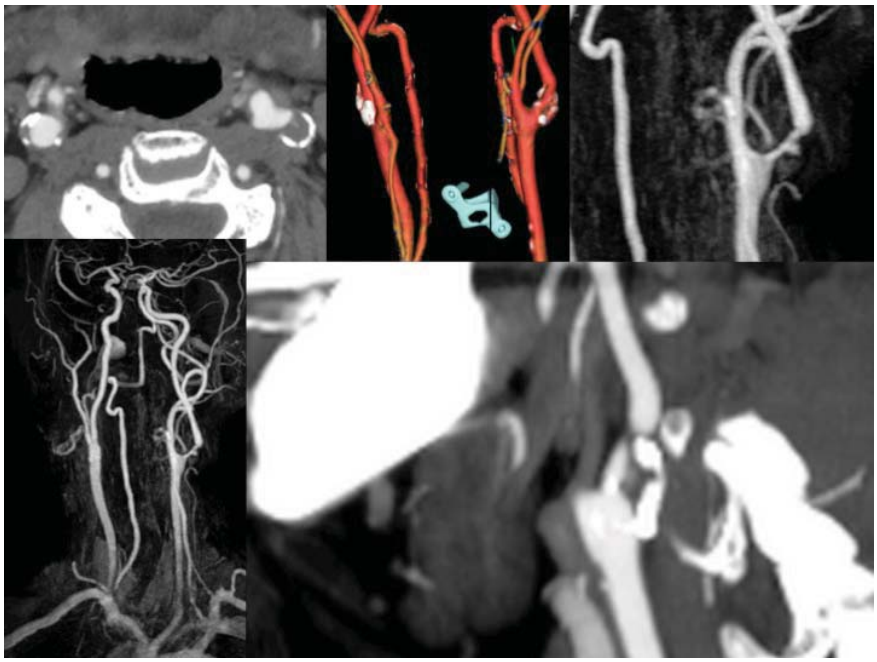


Fig. (3). High-grade carotid stenosis with ulceration.

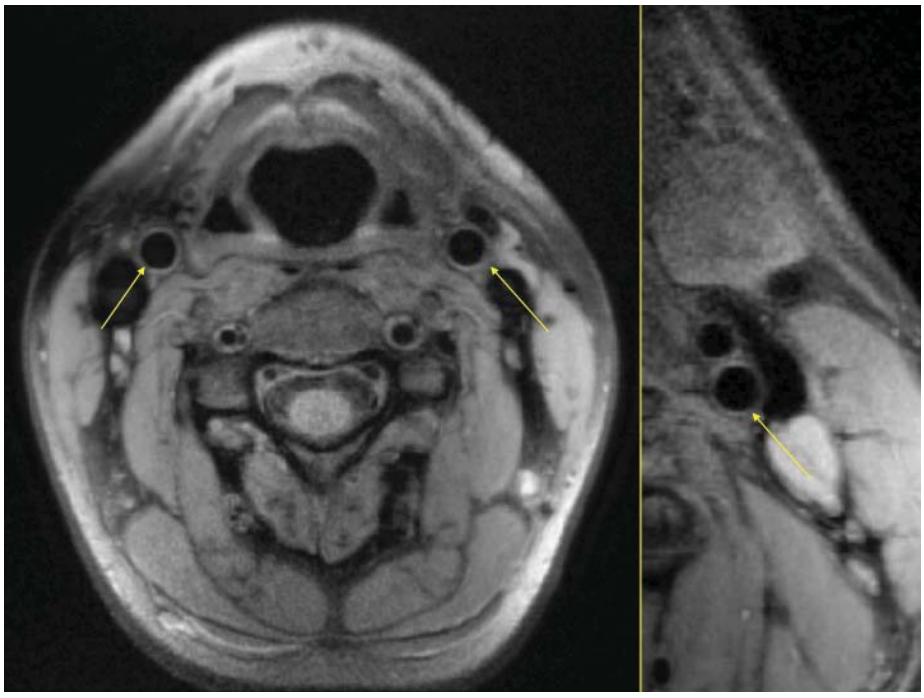
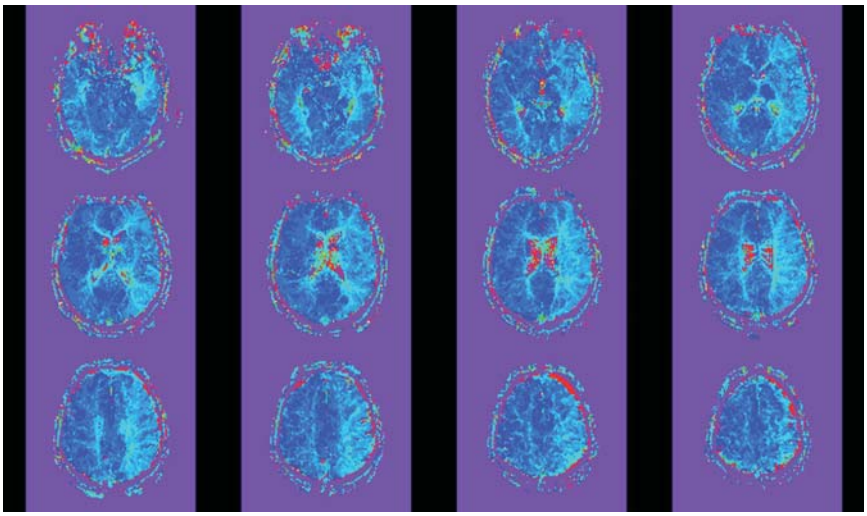


Fig. (4). High resolution axial MR I mages of the neck done at 3T with surface coils shows the carotid wall in detail (arrows).

ing of the vessels, even of the major vasculature, was hindered among others by a relatively low resolution and high susceptibility to motion-induces artifacts. With the introduction of contrast-enhanced MR angiography, this has changed since it has subsequently been possible to image the carotids fast with an excellent spatial resolution [13]. This has allowed to non-invasively obtain images of carotid and thus plaque morphology that allow us to explore the disease. A detailed image the carotid wall evaluated by MRI is shown in (Fig. **4**). While somewhat overestimating stenosis at times and being susceptible to flow phenomena rendering areas of turbulent flow not visible, MRA still has enormous potential for screening purposes. An example of dynamic contrast-enhanced MR perfusion is provided in (Fig. **5**). With the introduction of high-speed imaging, multi-channel coils and higher fields, it is possible to additionally visualize the brain parenchyma that is going to be affected in carotid stenosis [14] by both conventional means as well as by the use of more modern "functional" Neuro-MR techniques such as diffusion-weighted imaging and derived ADC mapping [15].



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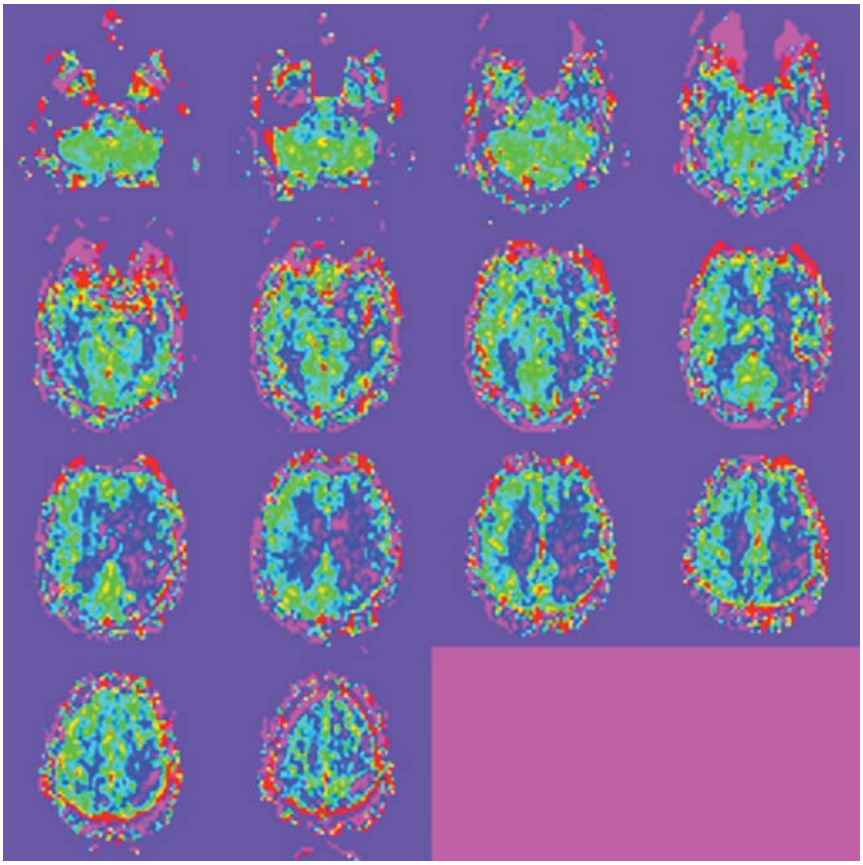

B

Fig. (5). Dynamic contrast-enhanced MR perfusion (**a**): Time to peak map compared to Arterial spin labeling MR perfusion (**b**) in a 82 year old patient with a left sided carotid stenosis.

Imaging of the plaque itself with MRI has been possible but is in itself not without problems [16]. The use of higher magnetic fields, while allowing higher signal and thus higher resolution and eventually magnification, in itself does not resolve everything since motion artifacts remain. Also the development of dedicated surface coils that allow to perform high-resolution imaging of t he carotid wall and plaque has not yet allowed this technique to enter the clinical arena since the use of these coils is time-consuming and may not be possible with all patients; however a very high degree of spatial resolution is possible.

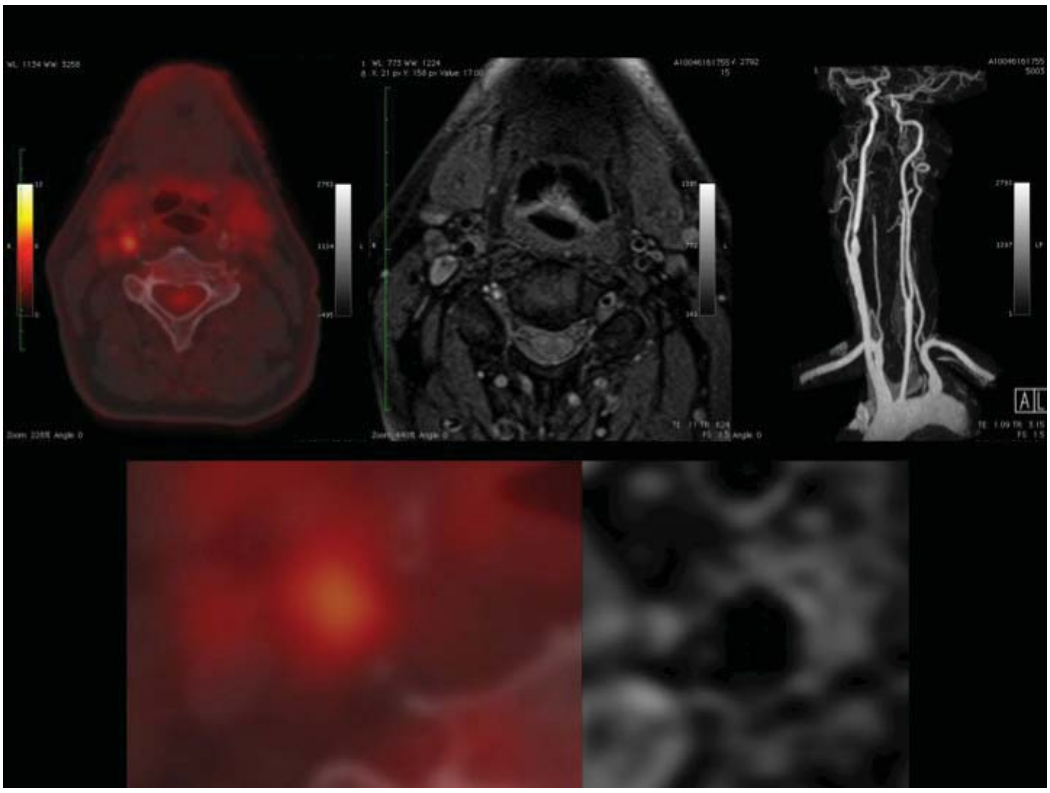

Fig. (6). 59-year old patient with a right-sided symptomatic stenosis. The PET CT shows hypercaptation in the right-sided carotid wall. MR shows a thickened carotid wall.

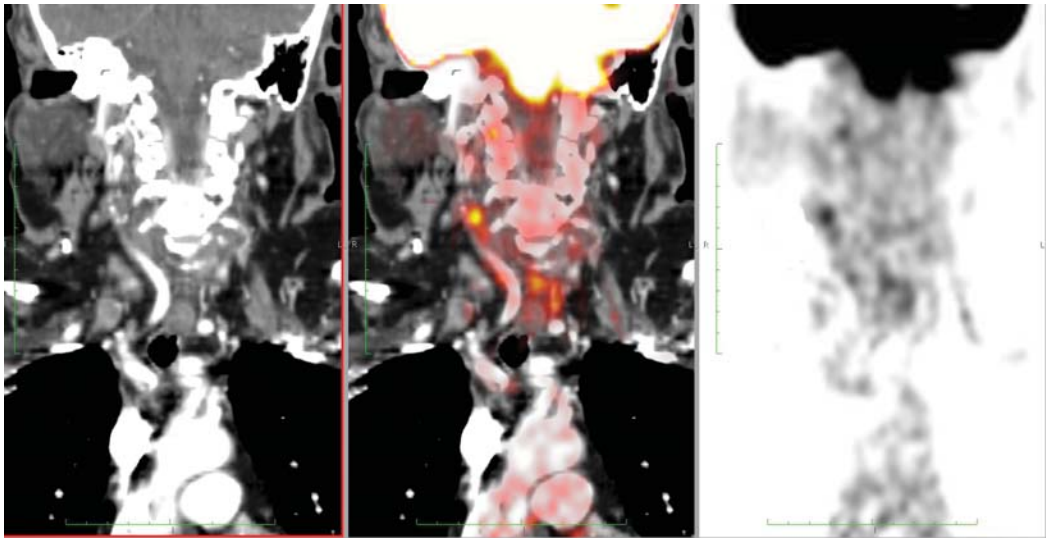

Fig. (7). Coronal CT reconstruction shows a complex plaque with calcific and soft plaque components; the PET shows hypercaptation in the plaque.

Visualizing the inflammatory process itself with the use of contrast agents has been tried and has met with variable success and levels of acceptance. Indeed, in addition to the traditional Gadolinium chelates that are currently used for post-contrast imaging in MRI, there has been some interest in developing a different approach using the paramagnetic properties of super paramagnetic iron oxide particles. These particles apparently accumulate lately in macrophages among other in various parts of the reticulo-endothelial system [17].

POSITRON EMISSION TOMOGRAPHY

Traditionally, nuclear medicine imaging with PET was used to image mainly cerebral degenerative diseases [18], to study brain activation or for oncologic purposes. The capacity of PET to detect inflammatory lesions is well known and has also been used for vascular purposes with some success [19]. It is mainly 18F-FDG PET that is going to be performed since it does seem to image inflammatory processes associated with an increased macrophagic activity [20].

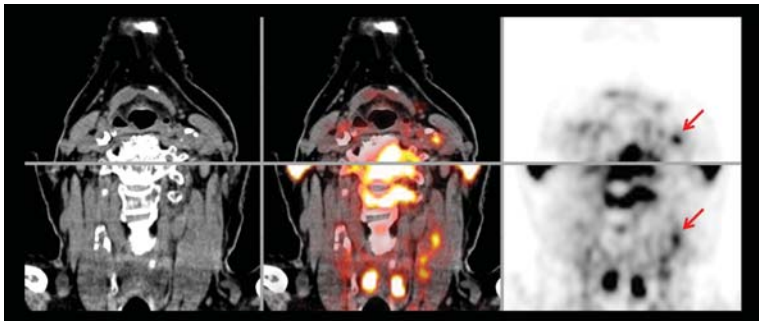

Fig. (8). Patient with high-grade carotid stenosis and renal insufficiency. He could not receive contrast. There is hyperactivity in the area of the suspected carotid plaque, signifying inflammation. Based on this, therapy could be proposed and initiated.

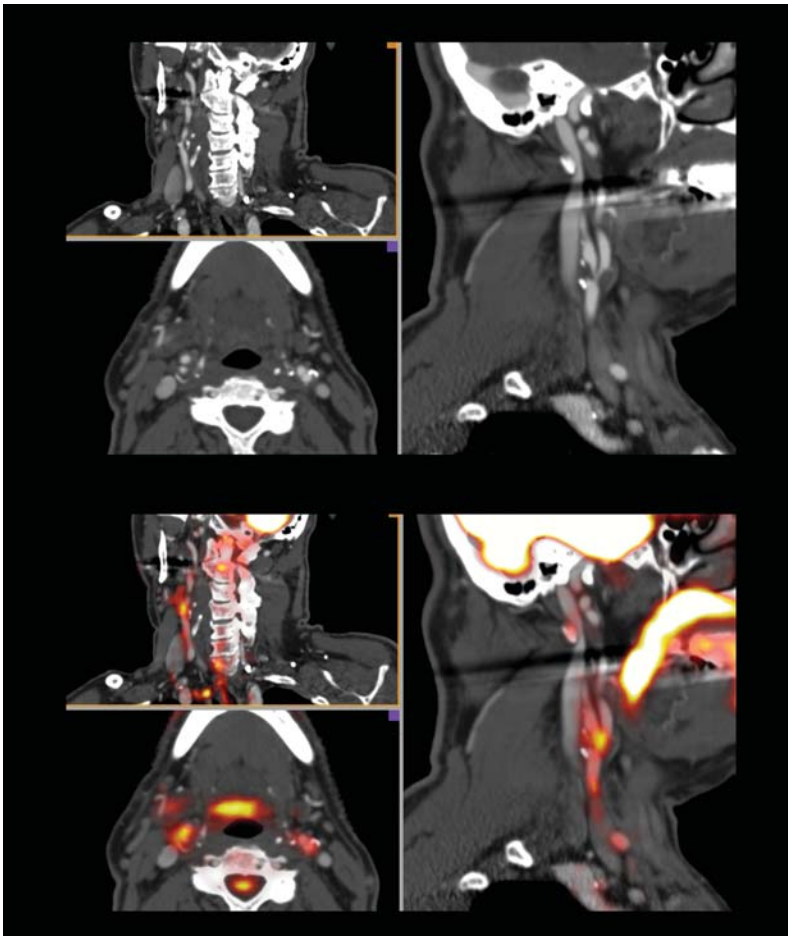

Fig. (9). PET-CT of inflammatory carotid artery disease.

From a technical point of view, Imaging is done 1 hour after injection of FDG [21, 22]. Also, Positron Emission Tomography has known an explosive development with the arrival of PET-CT scanners: whereas before the method had a somewhat limited application due to its relatively low spatial resolution, the capacity to perform at the same time anatomic and functional imaging was a real revolution; this is why PET-CT scanners have been widely deployed over the last decade. An area where PET imaging has also been used is in the assessment of carotid artery disease where a number of studies have shown its capacity to detect potentially inflammatory processes that underlie the embolic events [23]. A recent study seems to confirm that PET could be an early predictor of stroke recurrence and could thus be of help in selecting patients for early therapy [24]. Various examples of PET-CT images showing significant tracer uptake in the carotid wall are provided in (Figs. **6-10**). However, there is still some discussion as to whether the findings will guarantee that the method is superior to high-resolution CT [25]. This is in part due to a high variation in findings between CT, PET and MRI [26].

New perspectives are currently opened by a new hybrid modality, *i.e.* PET-MRI. It might be expected that combined PET and MRI imaging will allow obtaining complementary functional and morphological information, relevant for the

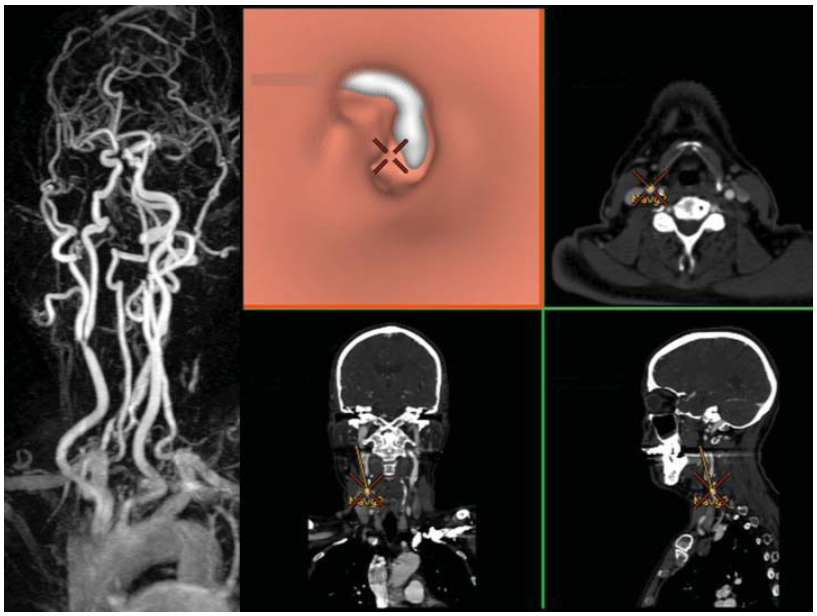

Fig. (10). Patient with severe right-sided carotid bifurcation stenosis seen on angio-MR. This is seen on the virtual endoscopic image.

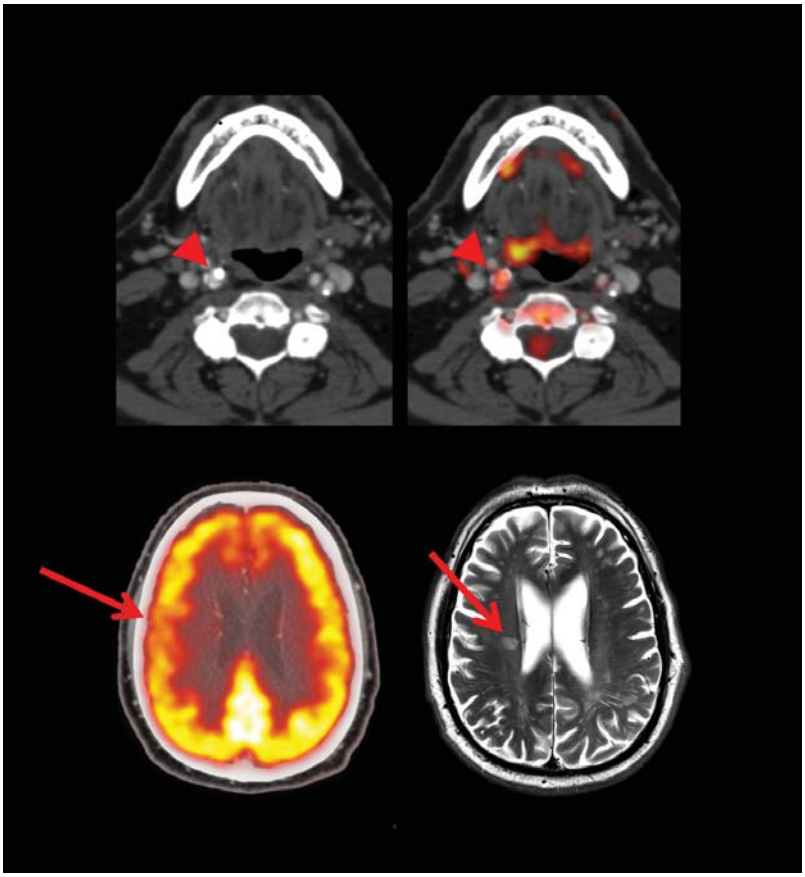

Fig. (11). Patient with right-sided calcific stenosis on the CTA; the PET overlay shows hypercaptation in the plaque; the PET at the level of the brain shows a right frontal hypoperfusion, and the MR image shows a constituted ischemic lesion (arrow).

evaluation of plaque activity and cerebrovascular disease, in a single imaging session, as suggested [27]. (Fig. **11**) shows an example of patient with an active carotid plaque and a concomitant ischemic lesion visible on brain MRI.

ANGIOGRAPHY

Catheter angiography remains the gold standard examination of the carotid artery. While its inherent role in diagnosis has diminished greatly over recent years due to improve-

ments in other diagnostic tools detailed above, it remains indispensable whenever an intervention is planned by endovascular means, or even sometimes surgery. While at the moment CEA is still the therapy of choice for patients with stenosis, there is still heated debate within neurointerventionalsts that stenting could have a m ore prominent role in the management of the disease.

Additionally, carotid angiography still remains the examination of choice if one wants to assess not just the presence of collateral vessels; while the presence of collaterals can be seen on CT and MRI, the presence or absence of flow and its directionality can be best assessed by direct angiography.

CONCLUSION

A better understanding of the mechanisms underlying and causing stroke and cerebrovascular diseases is going to have a major socio-economic impact that goes beyond a simple scientific understanding of the processes. Indeed, since it is associated with a high morbidity and mortality, stroke should be considered not just a target for acute interventions but for aggressive preventive measures. To these measures belongs besides effective treatment, improved means of visualizing the possible cause of embolism. After a thorough clinical examination, one is going to recommend an ultrasound that in addition to demonstrating changes in flow can also be used to investigate the morphology of the carotid wall as well as the plaque. Cerebral angiography, while still the "gold standard examination" and still the technique that allows to demonstrate in the best way any change in morphology will be more and more used whenever an interventional measure is envisioned and will be planned in the same session usually. The diagnostic work-up has been taken over by both MR and CT angiography techniques that have the advantage of covering the vasculature and the cerebral tissue, thus allowing the clinician to perform an overall assessment of not just the vessels but also of the state of the brain. Additionally to this, whenever doubt exists to the possible vulnerability of a plaque due to eventual inflammation [28], there is the possibility to perform either PET-CT or even high-resolution MR imaging of the plaque. These techniques, alone or in combination, such as is now possible with PET-MR in select centers, should allow to guide the clinician to a best adapted solution to the question as whether a plaque is responsible for the clinical symptom at hand. Then, together with results from systemic laboratory values, it will be possible for the clinician to decide whether to treat or not and what therapeutic methods to se, medical versus surgical versus endovascular. Thus, at least where carotid stenosis is considered, we have reached a moment when multimodality imaging allows us to combine high-resolution techniques such as fine-slice CT, High speed MRI with molecular functional techniques that depict plaque physiology [29].

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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