Mini Review

Imaging the carotid atherosclerotic plaque

Sandra Neumann¹, Elena G Milano²,³, Chiara Bucciarelli-Ducci¹,⁴,⁵, Giovanni Biglino¹,³,⁴,⁵

Affiliations

¹ Clinical Research and Imaging Centre (CRIC) Bristol, University of Bristol, UK
² UCL Institute of Cardiovascular Science and Great Ormond Street Hospital for Children, London, UK
³ Department of Surgery, Dentistry, Paediatrics and Gynaecology, University of Verona, Verona, Italy
⁴ University Hospitals Bristol, NHS Foundation Trust, Bristol, UK
⁵ Bristol Medical School, University of Bristol, Bristol, UK

Correspondence to: Dr Giovanni Biglino, Bristol Heart Institute, University Hospitals Bristol NHS Trust, Upper Maudlin Street, Bristol BS2 8HW, United Kingdom; email: g.biglino@bristol.ac.uk; telephone: +44 117 342 3287
Abstract

This mini review provides a concise overview of imaging techniques that are currently used to image the atherosclerotic plaque in the carotid artery in vivo. The main techniques include ultrasound imaging, X-ray imaging, magnetic resonance imaging and positron emission tomography imaging. Each technique has advantages and limitations and may be chosen depending on the availability, cost and clinical justification for its use. Common to all the imaging techniques presented here is the need for a skilled imaging professional to allow for high reliability and repeatability.

Whilst ultrasound-based imaging currently is regarded as a first line technique in clinical practice, the use of other techniques such as computed tomography angiography (CTA) or magnetic resonance angiography (MRA) need to be considered in presence of significant stenosis with or without symptoms. Advancements in these two modalities, as well as in PET imaging, are increasingly moving toward a better understanding of the risk-stratification and pre-interventional monitoring of patients at risk of plaque rupture as well as early identification of plaque development and better understanding of plaque composition (e.g. metabolic imaging).
Introduction

The study of the atherosclerotic plaque is of great interest for screening and assessment of patients at risk of cerebrovascular accidents (Finkel & Duffy, 2015). Several non-invasive imaging techniques can be used to study the atherosclerotic plaque. The plaque is typically composed of macrophage cells, fatty residue, calcium, and fibrous connective tissue and debris, causing a narrowing of the vessel lumen. The technique and modality chosen should be optimized for the study in question. This mini review aims to provide an overview of the techniques used to image non-invasively the carotid plaque in vivo. A summary of the techniques discussed is shown in figure 1.

Ultrasound-based imaging

Ultrasound-based imaging has the advantages of being non-invasive, radiation free, not requiring contrast-medium and associated to only minimal discomfort to the patient. The technique is cost-effective, widely available and allows both the visualization and the grading of the atherosclerotic plaque severity.

Carotid Intima-media thickness (CIMT) CIMT imaging uses a linear array transducer with a frequency of at least 7MHz in B-mode (Roman et al. 2006; Stein et al. 2008). Lower frequencies are not sufficient to obtain near-field resolution for the imaging of superficial vessels such as the carotid artery. The transducer angle should be standardized by means of external landmarks and measures should be taken through at least 2 complementary directions. From such data, the maximum and mean thickness of intima-media can be taken, as well as measurements of the lumen diameter. It is recommended that semi-automated edge detection software be used to identify the borders (Stein et al. 2008; Mac Ananey et al. 2014).

Thorough guidelines on the use and measurement of CIMT have been published, including percentile CIMT data by sex, age, and ethnicity (Stein et al. 2008) allowing for standardization of the method as well as reference ranges to be calculated for smaller studies. CIMT imaging has been validated against in vitro histology (Pignoli et al. 1986; Persson et al. 1994).

Success rates for imaging the common carotid is >90%, in the bifurcation is 64-77%, and in the internal carotid 31-48% (Howard et al. 1993; Del Sol et al. 2001). B-mode ultrasonography can more readily identify non-obstructive plaques than Doppler ultrasound, given that Doppler velocity does not increase significantly until >50%
lumen obstruction is observed. However, it should be noted that whilst there is good
agreement on the morphological evaluation of plaques, measurements of plaque
thickness is subject to a higher incidence of measurement error (Joakimson et al.
1997).

3D ultrasound
Serial 2D ultrasound images can be computed to reconstruct the 3D volume. This
requires specialized software and probes, but gives the advantages of reducing
operator variability as well as allowing for the visualization of both the thickness and
length of the plaque (Cires-Drouet et al. 2017). 3D ultrasound is more sensitive to
detect changes in plaque area (AlMuhanna et al. 2015).

Pixel Distribution Analysis (PDA)
A limitation of CIMT scans is that no reliable characterization of plaque composition,
and therefore stability, is available. Nevertheless, such techniques are under
development and are currently available for research purposes. For example, it has
been shown using PDA that the necrotic core of an unstable plaque is closer to the
lumen and appears hypoechoic (Kakkos et al. 2013). PDA uses grey-scale image
segmentation to map pixel brightness ranges across normalized longitudinal images.
The result is a percentage composition of tissue composition in the plaque, including
calcium, lipid and fibrous tissue. PDA can also provide information on the lipid core
size and location (Lal et al. 2006).

Contrast-enhanced ultrasonography (CEUS)
Whilst most of the time US assessment of the carotid arteries is performed entirely
non-invasively, image quality can be enhanced by the use of a contrast agent. For
CEUS, the contrast is typically microbubbles of an inert gas stabilized by a
phospholipid shell (e.g. sulphur hexafluoride or octafluoropropane). For carotid
CEUS, the carotid lumen and adventitia are enhanced, making luminal irregularities
more readily detectable. Late-phase enhancement (6 minutes after contrast
administration) suggests an increased inflammatory cell load within the plaque,
representing a possible marker for early plaque rupture (Moreno et al. 1994; Owen et
al. 2010). Careful evaluation of the patient medical history is needed before
administration of contrast given the range of contraindications (Huang et al. 2016).

X-ray based imaging
Computed tomography angiography (CTA)

Computed tomography angiography offers a fast acquisition (~10s) imaging modality. With the advent of multi-detector row computed tomography (MDCT) the ability and quality of non-invasive angiograms has substantially increased; CTA has a spatial resolution of approximately 0.5-1mm, but a relatively slow temporal resolution at 240-420ms. However, newer dual-source CT (DSCT) scans may reduce the temporal resolution to ~65ms, thereby making it near equivalent to that of magnetic resonance scans (Adamson & Newby 2018). Furthermore, DSCT allows for more accurate assessment of calcified plaque volume, as it uses two x-ray sources with different energies to achieve more detailed Hounsfield unit measurements (Das et al. 2009). Plaques are typically imaged using bolus-tracking CTA. Calcification, lipid content and fibrous tissue are classified based on voxel Hounsfield units (Ajduk et al. 2009). However, densely calcified plaques may result in beam hardening artefacts. Histopathological comparisons to DSCT show high agreement for the AHA classification of plaques, although it should be noted that type I and II lesions were seen only in histopathological analyses (Das et al. 2009). Risks associated with radiation exposure and iodinated contrast administration should be taken into account before performing CTA (Valentin 2000; Abbara et al. 2016).

Magnetic resonance-based Imaging

Magnetic resonance angiography (MRA)

A range of MR techniques have been developed with specific technical advantages for imaging of different components of the plaque (Singh et al. 2016). Visualization of head and neck vessels including the carotid arteries in the research setting is typically performed using time-of-flight MRA, but other non-contrast MR imaging sequences may be of interest. MR imaging have the ability not only to quantify vessel lumen but also, to characterize plaque composition including the necrotic core and calcification (Cai et al. 2002), fibrous cap (Hatsukami et al. 2000) and inflammation (Kerwin et al. 2006). A commonly used research technique for plaque imaging is the double inversion recovery or “black-blood” method. This uses a fast spin-echo sequence with double inversion recovery preparatory pulses resulting in a high contrast between the lumen and vessel wall. Newer sequences allow for the 3D acquisition so that the entire cervical carotid artery can be covered at a <1mm\(^3\) resolution in less than 2 minutes (Balu et al. 2011). Moreover, fat suppression
provides a clearer image and is essential for characterization of the plaque morphology. MRA can provide visualization of the vessel lumen, even when the vessel is highly calcified. However, the acquisition time is significantly longer than for CTA, and MRA has a relatively low spatial resolution (typically >1 mm). Nevertheless, MRA may be successfully used when CTA is contraindicated.

Recent advances in the application of $T_2$ mapping techniques (Basiolli et al. 2013) have made high-resolution, non-contrast enhanced plaque lipid quantification possible across the whole plaque area. The technique maps the $T_2$ decay on a voxel-by-voxel basis, is validated against histological samples, and has been shown able to distinguish recently symptomatic plaque with high sensitivity and specificity (Chai et al. 2017).

**Contrast enhanced magnetic resonance angiography (CE-MRA)**

CE-MRA is a contrast-enhanced technique, typically using gadolinium or iron oxide-based contrast media (rather than iodine-based contrast used in CTA). Contrast-MR may provide a clearer image of vessel morphology and plaques than non-contrast MR. To achieve this, calculations on the arrival time of the bolus is essential; imaging too early would yield an inadequate visualization of the vascular tree, whereas imaging too late may cause some contrast to spill into the venous system thereby adding noise to the anatomy under investigation (Maki et al. 2003). CE-MRA in the research setting may also be used to study preclinical and molecular imaging of the plaque. For a comprehensive review of CE-MRA see Makowski & Botnar (2013).

**Other Imaging techniques**

**Positron emission tomography-based Imaging**

Positron emission tomography (PET) uses targeted radio-tagged molecular probes, which undergo beta-decay. Whilst PET scans have traditionally suffered the same limitations as MRA, *i.e.* long acquisition time and limited spatial resolution, newer hybrid PET-CT and PET-MR scanners have made PET imaging an option for studying plaques in further depth, combining the anatomical and/or metabolic images with specific markers, *e.g.* for inflammation and hypoxia (Folco et al. 2011; Vesey et al. 2016).

**Summary**
This mini review has briefly presented the main non-invasive imaging techniques to visualise the carotid plaque *in vivo*. Each technique has advantages and limitations and may be chosen depending on the availability, cost and clinical justification for its use. Common to all the imaging techniques presented here is the need for a skilled imaging professional to allow for high reliability and repeatability. Whilst ultrasound-based imaging certainly is considered a first line technique in clinical practice, the use of CTA or MRA needs to be considered in presence of significant stenosis with or without symptoms. MRA, CTA and PET are moving us towards a better understanding of the risk-stratification and pre-interventional monitoring of patients at risk of plaque rupture as well as early identification of plaque development.

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**Conflict of interest**

CBD is a consultant for Circle Cardiovascular Imaging (Calgary, Canada). No other conflict of interest to declare.
References


carotid plaques: ultrasound *Semin Vasc Surg* 30(1): 44-53

Das M, Braunschweig T, Mühlenbruch G, Mahnken AH, Krings T, Langer S, Koeppel
of dual-source computed tomography (CT) findings and histopathological correlation
*Eur J Vasc Endovasc Surg* 38(1): 14-19

Del Sol AI, Moons KG, Hollander M, Hofman A, Koudstaal PJ, Groebbee DE,
in cardiovascular disease risk management? The Rotterdam Study *Stroke* 32(7):
1532-1538

Folco EJ, Sheikine Y, Rocha VZ, Christen T, Scvartz E, Sukhova GK, Di Carli MF,
Libby P (2011) Hypoxia but not inflammation augments glucose uptake in human
macrophages: Implications for imaging atherosclerosis with 18-fluorine-labelled 2-
deoxy-D-glucose positron emission tomography *J Am Coll Cardiol* 58(6): 603-614

shifts in managing atherosclerotic cardiovascular disease risk *Trends Cardiovasc
Med* 25(4): 340-347

thickness and rupture in human atherosclerotic carotid plaque in vivo with high-
resolution magnetic resonance imaging *Circulation* 102(9): 959-964

Howard G, Sharrett AR, Heiss G, Evans GW, Chambless LE, Riley WA, Burke GL
(1993) Carotid artery intimal-medial thickness distribution in general populations as
evaluated by B-mode ultrasound. ARIC Investigators. *Stroke* 24(9): 1297-1304

Huang DY, Yusuf GT, Daneshi M, Husainy MA, Ramnarine R, Sellars ME, Sidhu PS
(2017) Contrast-enhanced US-guided interventions: improving success rate and
avoiding complications using US contrast agents *Radiographics* 37(2): 652-664

assessment of carotid plaque occurrence, thickness and morphology. The Tromsø


**Figure legends**

Figure 1 - Summary of imaging techniques and relative advantages. MRI = magnetic resonance imaging, PET = positron emission tomography.

Figure 2 - A: Example of ultrasound-acquired images of the common carotid with B-mode non-contrast enhanced ultrasonography and visualisation of intima-media thickness in the near wall (NW) and far wall (FW); B: example of near wall and far wall visualisation using contrast-enhanced ultrasound imaging. Images modified from Shah et al. 2017.

Figure 3 – Example of plaque imaging by computed tomography angiogram in the common carotid artery with classification overlay to show non-calcified plaque (red) and calcified plaque (yellow) from Ramanathan et al. 2019.

Figure 4: Example of segmentation of magnetic resonance angiography (MRA) data of the internal carotid artery (different views, A and B), including three-dimensional reconstruction to reveal carotid anatomy (C and D). Example of black blood imaging in the internal carotid, the red arrow indicating a region of intraplaque hemorrhage (E); image modified from Sigovan et al. 2017. Example of T2 mapping of atherosclerotic carotid plaque, the red arrow indicating a region of intraplaque hemorrhage (F); image modified from Qi et al. 2018.
<table>
<thead>
<tr>
<th>Advantages</th>
<th>Ultrasound</th>
<th>X-Ray</th>
<th>MRI</th>
<th>PET</th>
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<tr>
<td>✓ Availability ✓ Cost ✓ Plaque content ✓ Calcium sensitive ✓ Plaque content ✓ Metabolic activity ✓ Biomarker tags</td>
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<tr>
<td>Disadvantages</td>
<td>X Plaque content X Radiation X Time to acquire X Time to acquire</td>
<td>X Some contrast X Spatial resolution X Spatial resolution X Availability</td>
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Fig. 1

283x65mm (144 x 144 DPI)
Fig. 2

269x90mm (144 x 144 DPI)
Fig. 3

251x141mm (144 x 144 DPI)
Fig. 4

254x142mm (72 x 72 DPI)