MINI REVIEW

Imaging the carotid atherosclerotic plaque

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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. While ultrasound-based imaging currently is regarded as a first line technique in clinical practice, the use of other techniques such as computed tomography angiography or magnetic resonance angiography need to be considered in the presence of significant stenosis with or without symptoms. Advancements in these two modalities, as well as in positron emission tomography 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 (1). 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 Fig. 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. Examples of ultrasound imaging are shown in Fig. 2.

Carotid intima-media thickness

Carotid intima-media thickness (CIMT) imaging uses a linear array transducer with a frequency of at least 7MHz
in B-mode (2, 3). 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 two 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 (3, 4).

Thorough guidelines on the use and measurement of CIMT have been published, including percentile CIMT data by sex, age and ethnicity (3) 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 (5, 6).

Success rates for imaging the common carotid is >90%, in the bifurcation is 64–77%, and in the internal carotid 31–48% (7, 8). 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 while there is good agreement on the morphological evaluation of plaques, measurements of plaque thickness is subject to a higher incidence of measurement error (9).

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 (10). 3D ultrasound is more sensitive to detect changes in plaque area (11).

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 (12). PDA uses gray-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 (13).

**Contrast-enhanced ultrasonography**

While 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 contrast-enhanced ultrasonography (CEUS), the contrast is typically microbubbles of an inert gas stabilized by a phospholipid shell (e.g. sulfur hexafluoride or octafluoropropane). For carotid CEUS, the carotid lumen and adventitia are enhanced, making luminal irregularities more readily detectable. Late-phase enhancement (6 min after contrast administration) suggests an increased inflammatory cell load within the plaque, representing a possible marker for early plaque rupture (14, 15). Careful evaluation of the patient medical history is needed before administration of contrast given the range of contraindications (16).

**X-ray based imaging**

**Computed tomography angiography**

Computed tomography angiography (CTA) 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 0.5–1 mm, but a relatively slow temporal resolution at 240–420 ms. However, newer dual-source CT (DSCT) scans may reduce the temporal resolution to ~65 ms, thereby making it near equivalent to that of magnetic resonance scans (17). 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 (18). Plaques are typically imaged using bolus-tracking CTA. Calcification, lipid content and fibrous tissue are classified

**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). Reproduced from Ramanathan R, Dey D, Nørgaard BL, et al.; Carotid plaque composition by CT angiography in asymptomatic subjects: a head-to-head comparison to ultrasound; *European Radiology*, 2019 (34). Copyright 2019 John Wiley and Sons.
Magnetic resonance-based imaging

Magnetic resonance angiography

A range of MR techniques have been developed with specific technical advantages for imaging of different components of the plaque (22). Examples of different MR imaging techniques are shown in Fig. 4. 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 has the ability not only to quantify vessel lumen but also to characterize plaque composition including the necrotic core and calcification (23), fibrous cap (24) and inflammation (25). 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 <1 mm³ resolution in less than 2 min (26). 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 T₂ mapping techniques (27) have made high-resolution, non-contrast-enhanced plaque lipid quantification possible across the whole plaque area. The technique maps the T₂ 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 (28).
Contrast-enhanced magnetic resonance angiography

Contrast-enhanced magnetic resonance angiography (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 (29). 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 and Botnar (30).

Other imaging techniques

Positron emission tomography-based imaging

Positron emission tomography (PET) uses targeted radio-tagged molecular probes, which undergo beta-decay. While PET scans have traditionally suffered the same limitations as MRA, that is, 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, for example, for inflammation and hypoxia (31, 32).

Summary

This mini review has briefly presented the main non-invasive imaging techniques to visualize 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. While 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 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.

Declaration of interest

C B D is a consultant for Circle Cardiovascular Imaging (Calgary, Canada). The other authors have nothing to disclose.

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References

1 Finkel JB & Duffy D. 2013 ACC/AHA cholesterol treatment guideline: paradigm shifts in managing atherosclerotic cardiovascular disease risk. Trends in Cardiovascular Medicine 2015 25 340–347. (https://doi.org/10.1016/j.tcm.2014.10.015)
2 Roman MJ, Naqvi TZ, Gardin JM, Gerhard-Herman M, Jaff M, Mohler E, American Society of Echocardiography & Society of Vascular Medicine and Biology. Clinical application of noninvasive vascular ultrasound in cardiovascular risk stratification: a report from the American Society of Echocardiography and the Society of Vascular Medicine and Biology. Journal of the American Society of Echocardiography 2006 19 943–954. (https://doi.org/10.1016/j.echo.2006.04.020)
3 Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, Najjar SS, Rembold CM, Post WS & American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. Journal of the American Society of Echocardiography 2008 21 93–111; quiz 189–190. (https://doi.org/10.1016/j.echo.2007.11.011)
4 Mac Ananey O, Mellotte G & Maher V. Comparison of semi-automated and manual measurements of carotid intima-media thickening. BioMed Research International 2014 2014 531389. (https://doi.org/10.1155/2014/531389)
5 Persson J, Formgren J, Israelsson B & Berglund G. Ultrasound-determined intima-media thickness and atherosclerosis. Direct and indirect validation. Arteriosclerosis and Thrombosis 1994 14 261–264. (https://doi.org/10.1161/01.ATV.14.2.261)
6 Pignoli P, Tremoli E, Poli A, Oreste P & Pasolletti R. Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. Circulation 1986 74 1399–1406. (https://doi.org/10.1161/01.ATV.14.2.261)
7 Del Sol AI, Moons KG, Hollander M, Hofman A, Koudstaal PJ, Grobbbee DE, Breteler MM, Witterman JC & Bots ML. Is carotid intima-media thickness useful in cardiovascular disease risk management? The Rotterdam Study. Stroke 2001 32 1532–1538. (https://doi.org/10.1161/01.STR.32.7.1532)
8 Howard G, Sharrett AR, Heiss G, Evans GW, Chambless LE, Riley WA & Burke GL. Carotid artery intimal-medial thickness distribution in general populations as evaluated by B-mode ultrasound. ARIC Investigators. Stroke 1993 24 1297–1304. (https://doi.org/10.1161/01.STR.24.9.1297)
9 Joakimson O, Bonaa KH & Stensland-Bugge E. Reproducibility of ultrasound assessment of carotid plaque occurrence, thickness and morphology. Stroke 1997 28 2201–2207. (https://doi.org/10.1161/01.STR.28.11.2201)
