MINI REVIEW

Imaging the carotid atherosclerotic plaque

Sandra Neumann[1],*, Elena G Milano[2,3], Chiara Bucciarelli-Ducci[1,4,5] and **Giovanni Biglino[1,3,4,5]**

[1]Research and Imaging Centre (CRIC) Bristol, University of Bristol, 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

*(S Neumann is now at Bristol Medical School, University of Bristol, Bristol, UK)

Correspondence should be addressed to G Biglino: g.biglino@bristol.ac.uk

Abstract

This mini review provides a concise overview of imaging techniques that are currently used to image the atheroscletoric 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).

Key Words
- ▶ imaging
- ▶ cardiology
- ▶ vascular disease

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 7 MHz

	Ultrasound	X-Ray	MRI	PET
Advantages	✓ Availability	✓ Fast	✓ Plaque content	✓ Metabolic activity
	✓ Cost	✓ Calcium sensitive	✓ High resolution	✓ Biomarker tags
Disadvantages	✗ Plaque content	✗ Radiation	✗ Time to acquire	✗ Time to acquire
	✗ Some contrast	✗ Spatial resolution	✗ Spatial resolution	✗ Availability

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

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
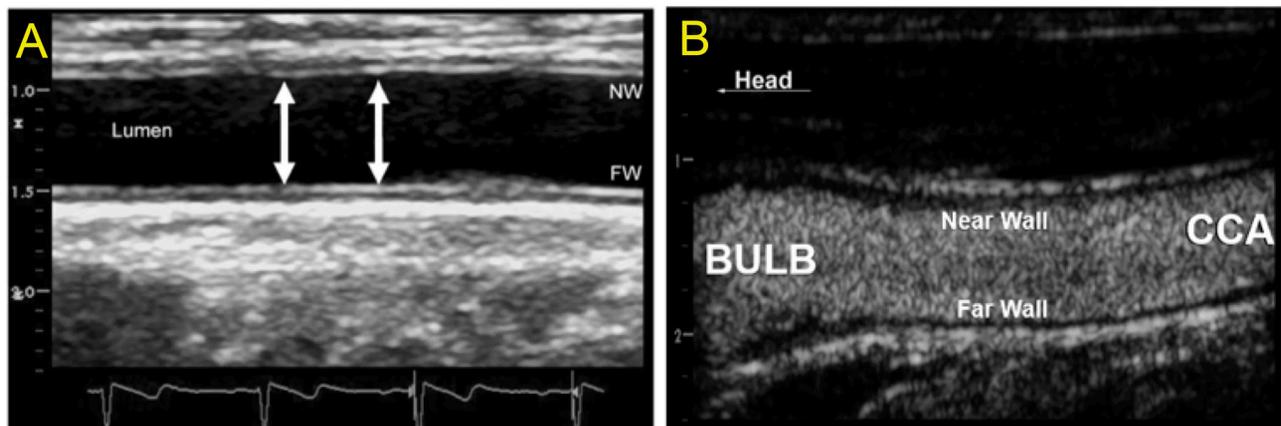

Figure 2
(A) Example of ultrasound-acquired images of the common carotid with B-mode non-contrast-enhanced ultrasonography and visualization of intima-media thickness in the near wall (NW) and far wall (FW); (B) example of near wall and far wall visualization using contrast-enhanced ultrasound imaging. Reproduced from Shah BN, Chahal NS, Kooner JS & Senior R; Contrast-enhanced ultrasonography vs B-mode ultrasound for visualization of intima-media thickness and detection of plaques in human carotid arteries; *Echocardiography* 2017, volume **34**, pages 723–730 (33). Copyright 2017 John Wiley and Sons.

VascularBiology

S Neumann *et al.*

Imaging the carotid
atherosclerotic plaque

1:1

H55

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 (~10 s) 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
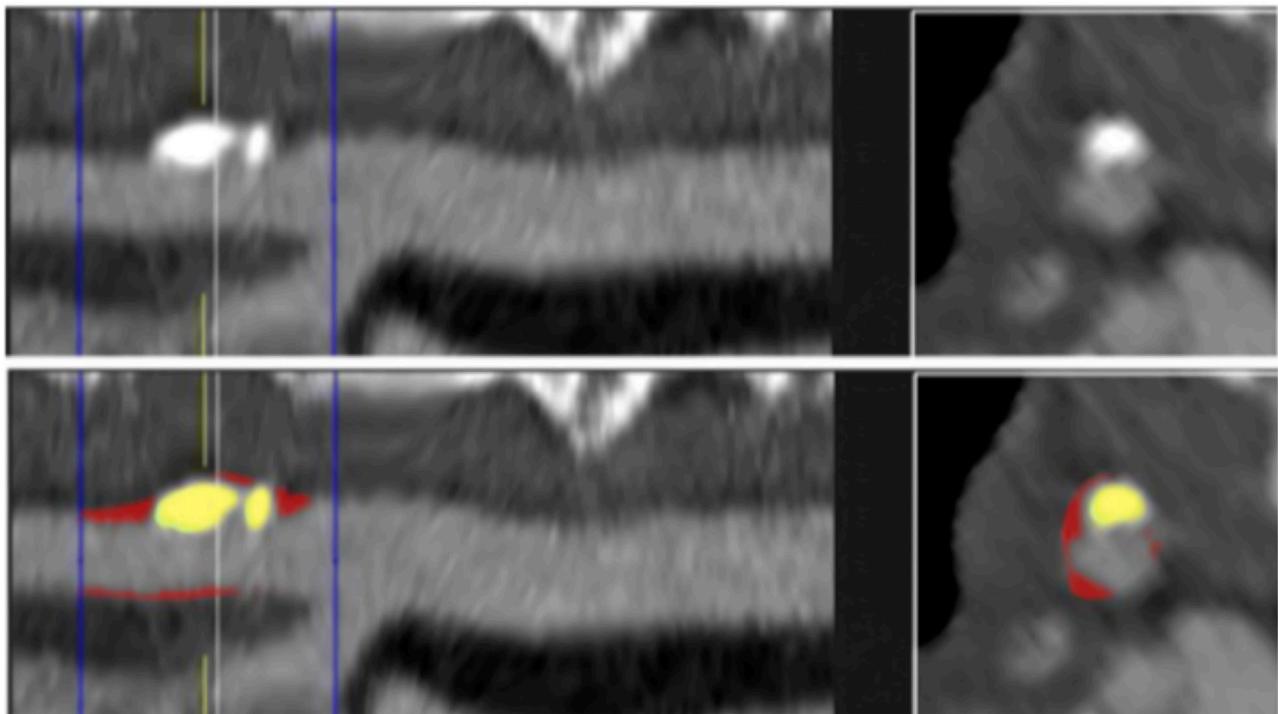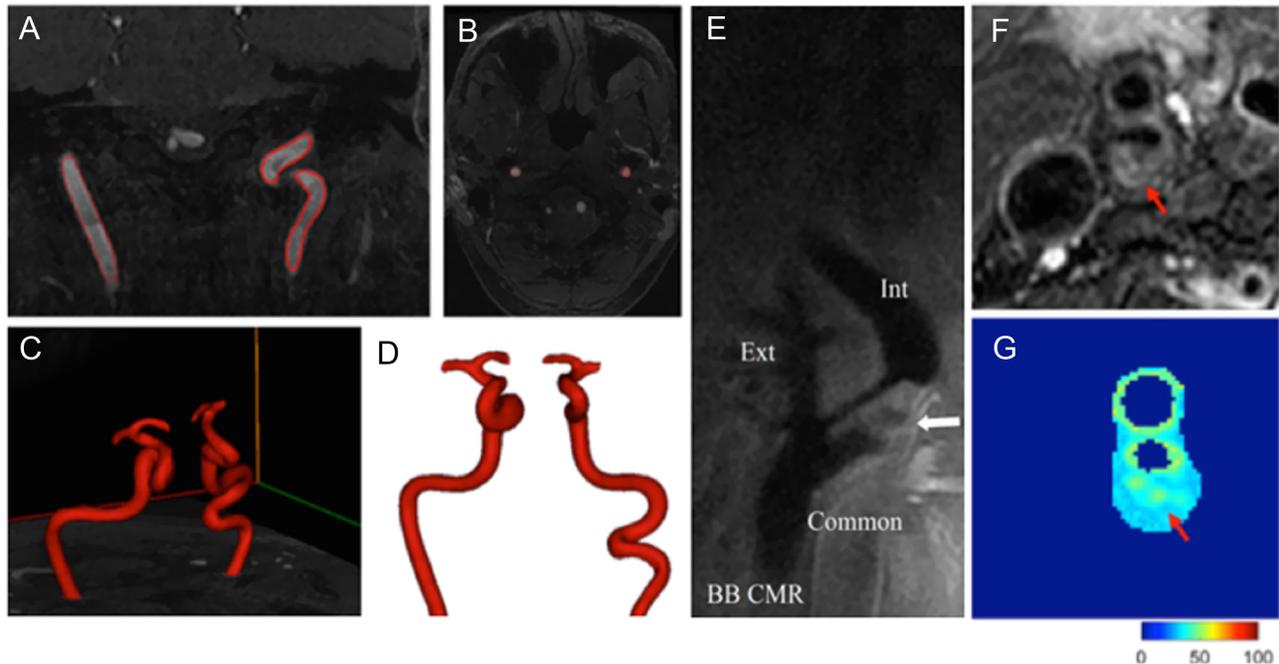

Figure 3

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.

Figure 4

Example of segmentation of magnetic resonance angiography (MRA) data of the internal carotid artery (different views, A and B), including 3D 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) (reproduced from Yu *et al*. under the terms of the original Creative Commons CCBY Attribution License (35)). Example of T2 mapping of atherosclerotic carotid plaque, the red arrow indicating a region of intraplaque hemorrhage (F) (reproduced from Qi H, Sun J, Qiao H, *et al*.; Simultaneous T1 and T2 mapping of the carotid plaque (SIMPLE) with T2 and inversion recovery prepared 3D radial imaging; *Magnetic Resonance in Medicine*, 2018 volume **80**, pages 2598–2608 (36); copyright 2018 John Wiley and Sons), which is shown mapped in (G).

based on voxel Hounsfield units (19). However, densely calcified plaques may result in beam-hardening artifacts. 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 (18). Risks associated with radiation exposure and iodinated contrast administration should be taken into account before performing CTA (20, 21). An example of CTA imaging is shown in Fig. 3.

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 T_2 mapping techniques (27) 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 (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.

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 & Paoletti 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.cir.74.6.1399)

7 Del Sol AI, Moons KG, Hollander M, Hofman A, Koudstaal PJ, Groebbee 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, Bønaa 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)

VascularBiology

S Neumann *et al.*

Imaging the carotid
atherosclerotic plaque

1:1

H58

10 Cires-Drouet RS, Mozafarian M, Ali A, Sikdar S & Lal BK. Imaging of high-risk carotid plaques: ultrasound. *Seminars in Vascular Surgery* 2017 **30** 44–53. (https://doi.org/10.1053/j.semvascsurg.2017.04.010)

11 AlMuhanna K, Hossain MM, Zhao L, Fischell J, Kowalewski G, Dux M, Sikdar S & Lal BK. Carotid plaque morphometric assessment with three-dimensional ultrasound imaging. *Journal of Vascular Surgery* 2015 **61** 690–697. (https://doi.org/10.1016/j.jvs.2014.10.003)

12 Kakkos SK, Griffin MB, Nicolaides AN, Kyracou E, Sabetai MM, Tegos T, Makris GC, Thomas DJ, Geroulakos G & Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group. The size of juxtaluminal hypoechoic area in ultrasound images of asymptomatic carotid plaques predicts the occurrence of stroke. *Journal of Vascular Surgery* 2013 **57** 609.e1–618.e1; discussion 617. (https://doi.org/10.1016/j.jvs.2012.09.045)

13 Lal BK, Hobson 2nd RW, Hameed M, Pappas PJ, Padberg Jr FT, Jamil Z & Durán WN. Noninvasive identification of the unstable plaque. *Annals of Vascular Surgery* 2006 **20** 167–174. (https://doi.org/10.1007/s10016-006-9000-8)

14 Moreno PR, Falk E, Palacios IF, Newell JB, Fuster V & Fallon JT. Macrophage infiltration in acute coronary syndrome. Implications for plaque rupture. *Circulation* 1994 **90** 775–778. (https://doi.org/10.1161/01.cir.90.2.775)

15 Owen DR, Shalhoub J, Miller S, Gauthier T, Doryforou O, Davies AH & Leen EL. Inflammation within carotid atherosclerotic plaque: assessment with late-phase contrast-enhanced US. *Radiology* 2010 **255** 638–644. (https://doi.org/10.1148/radiol.10091365)

16 Huang DY, Yusuf GT, Daneshi M, Husainy MA, Ramnarine R, Sellars ME & Sidhu PS. Contrast-enhanced US-guided interventions: improving success rate and avoiding complications using US contrast agents. *RadioGraphics* 2017 **37** 652–664. (https://doi.org/10.1148/rg.2017160123)

17 Adamson PD & Newby DE. Non-invasive imaging of the coronary arteries. *European Heart Journal* 2018 ehy670. (https://doi.org/10.1093/eurheartj/ehy670)

18 Das M, Braunschweig T, Mühlenbruch G, Mahnken AH, Krings T, Langer S, Koeppel T, Jacobs M, Günther RW & Mommertz G. Carotid plaque analysis: comparison of dual-source computed tomography (CT) findings and histopathological correlation. *European Journal of Vascular and Endovascular Surgery* 2009 **38** 14–19. (https://doi.org/10.1016/j.ejvs.2009.03.013)

19 Ajduk M, Pavić L, Bulimbasić S, Sarlija M, Pavić P, Patrlj L & Brkljacić B. Mulitdetector-row computed tomography in evaluation of atherosclerotic plaques complicated with intraplaque haemorrhage. *Annals of Vascular Surgery* 2009 **23** 186–193. (https://doi.org/10.1016/j.avsg.2008.05.008)

20 Abbara S, Blanke P, Maroules CD, Cheezum M, Choi AD, Han BK, Marwan M, Naoum C, Norgaard BL, Rubenstein R, *et al.* SCCT guidelines for the performance and acquisition of coronary computed tomographic angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee: endorsed by the North American Society for Cardiovascular Imaging (NASCI). *Journal of Cardiovascular Computed Tomography* 2016 **10** 435–449. (https://doi.org/10.1016/j.jcct.2016.10.002)

21 Valentin J. Pregnancy and medical radiation: ICRP Publication 84. *Annals of the ICRP* 2000 **30** 1–39.

22 Singh N, Moody AR, Roifman I, Bluemke DA & Zavodni AE. Advanced MRI for carotid plaque imaging. *International Journal of Cardiovascular Imaging* 2016 **32** 83–89. (https://doi.org/10.1007/s10554-015-0743-6)

23 Cai JM, Hatsukami TS, Ferguson MS, Small R, Polissar NL & Yuan C. Classification of human carotid atherosclerotic lesions with in vivo multicontrast magnetic resonance imaging. *Circulation* 2002 **106** 1368–1373. (https://doi.org/10.1161/01.cir.0000028591.44554.f9)

24 Hatsukami TS, Ross R, Polissar NL & Yuan C. Visualisation of fibrous cap thickness and rupture in human atherosclerotic carotid plaque in vivo with high-resolution magnetic resonance imaging. *Circulation* 2000 **102** 959–964. (https://doi.org/10.1161/01.cir.102.9.959)

25 Kerwin WS, O'Brien KD, Ferguson MS, Polissar N, Hatsukami TS & Yuan C. Inflammation in carotid atherosclerotic plaque: a dynamic contrast-enhanced MR imaging study. *Radiology* 2006 **241** 459–468. (https://doi.org/10.1148/radiol.2412051336)

26 Balu N, Yarnykh VL, Chu B, Wang J, Hatsukami T & Yuan C. Carotid plaque assessment using fast 3D isotropic resolution black-blood MRI. *Magnetic Resonance in Medicine* 2011 **65** 627–637. (https://doi.org/10.1002/mrm.22642)

27 Basiolli L, Lindsay AC, Chai JT, Choudhury RP & Robson MD. In-vivo quantitative T_2 mapping of carotid arteries in atherosclerotic patients: segmentation and T_2 measurement of plaque components. *Journal of Cardiovascular Magnetic Resonance* 2013 **15** 69. (https://doi.org/10.1186/1532-429X-15-69)

28 Chai JT, Basiolli L, Li L, Alkhalil M, Galassi F, Darby C, Halliday AW, Hands L, Magee T, Perkins J, *et al.* Quantification of lipid-rich core in carotid atherosclerosis using magnetic resonance T_2 mapping: relation to clinical presentation. *JACC: Cardiovascular Imaging* 2017 **10** 747–756. (https://doi.org/10.1016/j.jcmg.2016.06.013)

29 Maki JH, Knopp MV & Prince M. Contrast-enhanced MR angiography. *Applied Radiology* 2003 182–210.

30 Makowski MR & Botnar RM. MR imaging of the arterial vessel wall: molecular imaging from bench to bedside. *Radiology* 2013 **269** 34–51. (https://doi.org/10.1148/radiol.13102336)

31 Folco EJ, Sheikine Y, Rocha VZ, Christen T, Scvartz E, Sukhova GK, Di Carli MF & Libby P. 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. *Journal of the American College of Cardiology* 2011 **58** 603–614. (https://doi.org/10.1016/j.jacc.2011.03.044)

32 Vesey AT, Dweck MR & Fayad ZA. Utility of combining PET and MR imaging of carotid plaque. *Neuroimaging Clinics of North America* 2016 **26** 55–68. (https://doi.org/10.1016/j.nic.2015.09.005)

33 Shah BN, Chahal NS, Kooner JS & Senior R. Contrast-enhanced ultrasonography vs B-mode ultrasound for visualization of intima-media thickness and detection of plaques in human carotid arteries. *Echocardiography* 2017 **34** 723–730. (https://doi.org/10.1111/echo.13513)

34 Ramanathan R, Dey D, Nørgaard BL, Goeller M, Bjerrum IS, Antulov R, Diederichsen ACP, Sidelmann JJ, Gram JB & Sand NPR. Carotid plaque composition by CT angiography in asymptomatic subjects: a head-to-head comparison to ultrasound. *European Radiology* 2019. (https://doi.org/10.1007/s00330-019-06086-y)

35 Yu W, Underhill HR, Ferguson MS, Hippe DS, Hatsukami TS, Yuan C & Chu B. The added value of longitudinal black-blood cardiovascular magnetic resonance angiography in the cross sectional identification of carotid atherosclerotic ulceration. *Journal of Cardiovascular Magnetic Resonance* 2009 **11** 31. (https://doi.org/10.1186/1532-429X-11-31)

36 Qi H, Sun J, Qiao H, Zhao X, Guo R, Balu N, Yuan C & Chen H. Simultaneous T1 and T2 mapping of the carotid plaque (SIMPLE) with T2 and inversion recovery prepared 3D radial imaging. *Magnetic Resonance in Medicine* 2018 **80** 2598–2608. (https://doi.org/10.1002/mrm.27361)