ISMRM 2015

Carotid Disease: What the Radiologist Provides

How tight? How bright? How brain?*

How tight?

The original publication in 1991 of the NASCET trial (1) provided clarity for the selection of patients for carotid surgery following a period when there was little strong evidence for the use of endarterectomy in the prevention of future cerebrovascular events. Over the ensuing twenty five years much of the radiologist's role has revolved around the accurate measurement of carotid stenosis, providing quantitative evidence regarding the patient's eligibility, or otherwise, for surgical treatment as defined by NASCET and other endarterectomy trials. Over the same time period vascular imaging has made giant strides such that the original gold standard of invasive catheter angiography, with its inherent morbidity and mortality, has largely been replaced by non-invasive imaging techniques. A combination of techniques is often employed, commonly using Doppler ultrasound as a means of detecting the flow disturbance caused by significant carotid stenosis, then to be confirmed by more anatomical imaging such as Magnetic Resonance Angiography (MRA). Concordant results from such tests are usually sufficient for surgical decision making (2). So what clinically useful information can the radiologist now provide to the clinician referring a patient to MRI?

First and foremost the patient is being referred for assessment of their carotid disease. Using NASCET criteria for the measurement of stenosis the region of interest that needs to be covered must not only include the carotid bifurcation but sufficient internal carotid artery above this level to allow consistent percent stenosis measurements. High resolution techniques are required for accurate stenosis assessment. Considering an internal carotid artery diameter of approximately 5mm, it is necessary to be able to detect a stenosed luminal diameter of less than 1.5mm and so resolution should be sufficient to detect such changes (ie pixel size in the order of 0.3-0.4mm). While there are theoretical disadvantages of using Time Of Flight techniques to accurately measure high grade stenosis, due to turbulent flow resulting in stenosis overcall, the technique appears robust, perhaps due to the high-flow profile at the level of the stenosis maintaining TOF effects with little signal loss (3).

In the knowledge that atherosclerosis is not a focal condition, interrogation of the carotid system from the aortic arch to the circle of Willis is prudent if a patient is being considered for surgery to ensure no additional, contralateral or tandem lesions are present. Contrast enhanced MRA is a time effective way of surveying the whole of the anterior and posterior circulations to provide a comprehensive vascular examination. Combination of these TOF and contrast enhanced MRA will provide an accurate measure of stenosis and confirm, or not, the presence of anterior circulation disease. Occult aortic arch disease can be detected on the contrast enhanced angiogram along with contralateral or posterior circulation disease. Importantly, tandem disease ipsilateral to the index stenosis may be demonstrated which may have impact on the surgical decision making.

CEMRA has sufficient coverage that good views of the circle of Willis can be obtained and reconstructed in the axial plane from the 3D data set. This provides morphological information

regarding collateral circulation via the circle, or demonstrates an isolated anterior circulation due to circle variants. Phase contrast angiography of the circle of Willis provides more physiological directional flow information also helpful in surgical planning which involves the use of intra-operative carotid cross clamping or temporary carotid bypass. When near occlusion is detected the anatomy and physiology within the circle of Willis may play a role in patient management.

Near occlusion, representing a high level of stenosis (>95%), may be represented by the 'string sign' on angiographic imaging, denoting collapse of the internal carotid artery distal to the stenosis. Flow within this segment is markedly reduced and TOF techniques are limited due to decreased blood velocity. The contrast MRA technique, uninfluenced by the lack of flow, can therefore provide crucial information differentiating near occlusion from occlusion, the latter excluding surgical intervention. It should be noted that in vessels with significant stenosis (>70%), but "with the less profound appearance of near occlusion without threadlike collapses lumen" (4), there is hemodynamic compromise within the distal vessel causing a reduction of vessel caliber. The ratio of the stenotic carotid artery to the distal carotid artery will therefore be affected, and if unrecognized will result in an underestimate of the degree of stenosis.

How brain

Patients being investigated for carotid disease may benefit from a limited brain scan while they are undergoing MRA. For those previously presenting with cerebral symptoms, which sometimes are difficult clinically to definitely attribute to cerebral ischemia (5), brain imaging provides an opportunity to assess for prior ischemic damage in the appropriate territory which may influence the clinical decision regarding the need for surgery. The use of diffusion weighted imaging in the acute symptomatic phase provides the opportunity to directly visualize the index symptomatic brain lesion. In asymptomatic disease acute DWI lesions can sometimes be seen serendipitously. Patients with non-surgical carotid disease may demonstrate significant cerebro-ischemic disease requiring ongoing medical therapy to avoid further progression. This is important as the significance of vascular risk factors for development of vascular dementia is increasingly recognized (6). Patients who have already undergone CEMRA have the opportunity to also undergo post contrast T1 brain imaging to exclude an occult enhancing lesion with no need for additional contrast administration.

How bright

As described above, patients may be investigated because they have been found to have a carotid stenosis that needs more accurate stenosis assessment. Because carotid Doppler measurements give a range of values the MRA may confirm the stenosis but the patient may remain a non-surgical candidate as their stenosis is not sufficiently severe. Similarly, following an acute cerebral ischemic event, a patient's carotid arteries are investigated to try and identify whether carotid artery disease is the cause of the brain event, but a significant stenosis may not be found. However, previous studies such as TOAST (7) stated "the etiology of ischemic stroke affects prognosis, outcome and management". Within this study significant (causative) carotid artery disease was defined as a stenosis greater than 50%. Conversely a stenosis less than 50% was deemed non-contributory: "the diagnosis of stroke secondary to large artery atherosclerosis cannot be made if duplex or

arteriographic studies are normal or show only minimal changes". Even as this definition of causality was published, it was already known from the research carried out in the coronary vascular bed (8) that vascular events commonly arose from stenoses of less than 50%. From the European Carotid Surgical Trial (9,10), over 30% of the strokes that occurred in symptomatic patients were associated with a non-significant carotid stenosis, and this figure was even greater for the asymptomatic group. The TOAST classification would characterize many of these as stroke of undetermined origin, or cryptogenic. The reliance on stenosis to define significant carotid disease therefore likely results in significant false negative results.

In the last twenty years however the role of vessel wall disease, rather than luminal stenosis, has gained increased traction as the underlying cause of carotico-embolic disease (11). New imaging techniques to visualise the vessel wall directly, rather than the indirect effect vessel wall has on the lumen, have been increasingly refined and applied to understand the natural history of carotid atherosclerotic disease. These studies have shown MR imaging characteristics can predict plaque progression and also identify patients at increased risk of future cerebrovascular events. Lack of wide scale application of such techniques however has likely hinged on the fact that large, multicentre, outcome trials are lacking, whether they are used for selection of surgical candidates or patients for maximal medical therapy to treat atherosclerotic disease. Before the clinical community will invest in additional imaging time the outcome benefit of these techniques need to be demonstrated.

One plaque characteristic that has been shown to predict outcomes, in the research setting at least, is intraplaque hemorrhage (IPH). Even in 1999, it was shown that 5/20 patients presenting with DWI detected acute stroke, but with no significant (<50%) stenosis, demonstrated high signal intensity on MR within the carotid vessel wall ipsilateral to their stroke (12). In those patients the cause of stroke would have been classified as cryptogenic. The high signal (due to hemorrhage and methemoglobin formation) has subsequently been shown histologically to represent IPH (13). In subsequent studies IPH has been found to be related to neuro-ischemic events in patients with high (14) and moderate (15) grades of stenosis, whether previously symptomatic (16) or asymptomatic (17). IPH is seen in plaques that progress more rapidly (18) and recently in patients with progression of their percent carotid stenosis (19). IPH has also been related with spontaneous (20) and intraoperative emboli during carotid endarterectomy (21) and is associated with significant cerebral white matter disease (22). Early studies have suggested that patients with evidence of IPH have more imaging and clinical events if they undergo carotid stenting which may therefore influence choice of therapeutic intervention (23). Mirroring pathological studies (24), the mere presence of carotid IPH appears to define an individual as having a high-risk cardiovascular phenotype (25,26).

MR detected IPH therefore appears to be a useful imaging biomarker of high risk carotid atherosclerotic disease, which may result in a number of adverse outcomes over time. Wide clinical application of such a technique, even after appropriate outcome trials, will only be likely if the image acquisition time penalty, and therefore true financial cost, balances the clinical information that it provides. Fortunately, demonstration of this biomarker is relatively simple requiring no specialized hardware or software, and is applicable on all vendor platforms. Similarly, the interpretation of the imaging is also straightforward. Barriers to adoption of the technique, other than six minutes of imaging time, are therefore few.

Summary

A balance needs to be achieved between what the radiologist can provide and what the clinician needs, and the imaging protocol needs to be adapted accordingly. The simplest MRI request, but potentially delivering a truly comprehensive assessment for carotico-cerebral clinical management, can perhaps be summed up in six words: How tight? How bright? How brain? Combined, the answers to these questions will provide accurate measurement of the degree of carotid stenosis, characterization of vessel wall disease and detection of cerebral end organ disease. Together, these provide truly individualised clinical imaging, and will hopefully contribute to further understanding of the natural history of carotid atherosclerosis, its management and treatment.

***Acknowledgment: ST MacSweeney FRCS, Queen's Medical Centre, Nottingham, UK.**

References

1. Clinical alert: benefit of carotid endarterectomy for patients with high-grade stenosis of the internal carotid artery. National Institute of Neurological Disorders and Stroke Stroke and Trauma Division. North American Symptomatic Carotid Endarterectomy Trial (NASCET) investigators. Stroke; a journal of cerebral circulation 1991;22(6):816-817.

2. Ricotta JJ, Aburahma A, Ascher E, Eskandari M, Faries P, Lal BK. Updated Society for Vascular Surgery guidelines for management of extracranial carotid disease: executive summary. Journal of vascular surgery 2011;54(3):832-836.

3. Weber J, Veith P, Jung B, Ihorst G, Moske-Eick O, Meckel S, Urbach H, Taschner CA. MR Angiography at 3 Tesla to Assess Proximal Internal Carotid Artery Stenoses: Contrast-Enhanced or 3D Time-of-Flight MR Angiography? Clin Neuroradiol 2015;25(1):41-48.

4. Fox AJ, Eliasziw M, Rothwell PM, Schmidt MH, Warlow CP, Barnett HJ. Identification, prognosis, and management of patients with carotid artery near occlusion. AJNR American journal of neuroradiology 2005;26(8):2086-2094.

5. Allder SJ, Moody AR, Martel AL, Morgan PS, Delay GS, Gladman JR, Fentem P, Lennox GG. Limitations of clinical diagnosis in acute stroke. Lancet 1999;354(9189):1523.

6. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, Launer LJ, Laurent S, Lopez OL, Nyenhuis D, Petersen RC, Schneider JA, Tzourio C, Arnett DK, Bennett DA, Chui HC, Higashida RT, Lindquist R, Nilsson PM, Roman GC, Sellke FW, Seshadri S. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. Stroke; a journal of cerebral circulation 2011;42(9):2672-2713.

7. Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE, 3rd. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke; a journal of cerebral circulation 1993;24(1):35-41.

8. Ambrose JA, Winters SL, Arora RR, Haft JI, Goldstein J, Rentrop KP, Gorlin R, Fuster V. Coronary angiographic morphology in myocardial infarction: a link between the pathogenesis of unstable angina and myocardial infarction. Journal of the American College of Cardiology 1985;6(6):1233-1238.

9. Risk of stroke in the distribution of an asymptomatic carotid artery. The European Carotid Surgery Trialists Collaborative Group. Lancet 1995;345(8944):209-212.

10. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet 1998;351(9113):1379-1387.

11. Willinek WA. Looking beyond the lumen to predict cerebrovascular events: "the road less travelled by". Stroke; a journal of cerebral circulation 2006;37(3):759-760.

12. Moody AR, Allder S, Lennox G, Gladman J, Fentem P. Direct magnetic resonance imaging of carotid artery thrombus in acute stroke. The Lancet 1999;353(9147):122-123.

13. Moody AR, Murphy RE, Morgan PS, Martel AL, Delay GS, Allder S, MacSweeney ST, Tennant WG, Gladman J, Lowe J, Hunt BJ. Characterization of complicated carotid plaque with magnetic resonance direct thrombus imaging in patients with cerebral ischemia. Circulation 2003;107(24):3047-3052.

14. Altaf N, MacSweeney ST, Gladman J, Auer DP. Carotid intraplaque hemorrhage predicts recurrent symptoms in patients with high-grade carotid stenosis. Stroke; a journal of cerebral circulation 2007;38(5):1633-1635.

15. Altaf N, Daniels L, Morgan PS, Auer D, MacSweeney ST, Moody AR, Gladman JR. Detection of intraplaque hemorrhage by magnetic resonance imaging in symptomatic patients with mild to moderate carotid stenosis predicts recurrent neurological events. Journal of vascular surgery 2008;47(2):337-342.

16. Murphy RE, Moody AR, Morgan PS, Martel AL, Delay GS, Allder S, MacSweeney ST, Tennant WG, Gladman J, Lowe J, Hunt BJ. Prevalence of complicated carotid atheroma as detected by magnetic resonance direct thrombus imaging in patients with suspected carotid artery stenosis and previous acute cerebral ischemia. Circulation 2003;107(24):3053-3058.

17. Singh N, Moody AR, Gladstone DJ, Leung G, Ravikumar R, Zhan J, Maggisano R. Moderate carotid artery stenosis: MR imaging-depicted intraplaque hemorrhage predicts risk of cerebrovascular ischemic events in asymptomatic men. Radiology 2009;252(2):502-508.

18. Takaya N, Yuan C, Chu B, Saam T, Polissar NL, Jarvik GP, Isaac C, McDonough J, Natiello C, Small R, Ferguson MS, Hatsukami TS. Presence of intraplaque hemorrhage stimulates progression of carotid atherosclerotic plaques: a high-resolution magnetic resonance imaging study. Circulation 2005;111(21):2768-2775.

19. Singh N, Moody AR. Persistent Intraplaque Hemorrhage is Associated with the Progression of Preexisting Low and Moderate Grade Carotid Stenosis: Results of a 10-Year 3D Carotid MRI Clinical Experience. American Society of Neuroradiology, Chicago, IL, USA. 2015. O-452

20. Altaf N, Goode SD, Beech A, Gladman JR, Morgan PS, MacSweeney ST, Auer DP. Plaque hemorrhage is a marker of thromboembolic activity in patients with symptomatic carotid disease. Radiology 2011;258(2):538-545.

21. Altaf N, Beech A, Goode SD, Gladman JR, Moody AR, Auer DP, MacSweeney ST. Carotid intraplaque hemorrhage detected by magnetic resonance imaging predicts embolization during carotid endarterectomy. Journal of vascular surgery 2007;46(1):31-36.

22. Altaf N, Morgan PS, Moody A, MacSweeney ST, Gladman JR, Auer DP. Brain white matter hyperintensities are associated with carotid intraplaque hemorrhage. Radiology 2008;248(1):202-209.

23. Yoshimura S, Yamada K, Kawasaki M, Asano T, Kanematsu M, Miyai M, Enomoto Y, Egashira Y, Iwama T. Selection of carotid artery stenting or endarterectomy based on magnetic resonance plaque imaging reduced periprocedural adverse events. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association 2013;22(7):1082-1087.

24. Hellings WE, Peeters W, Moll FL, Piers SR, van Setten J, Van der Spek PJ, de Vries JP, Seldenrijk KA, De Bruin PC, Vink A, Velema E, de Kleijn DP, Pasterkamp G. Composition of carotid atherosclerotic plaque is associated with cardiovascular outcome: a prognostic study. Circulation 2010;121(17):1941-1950.

25. Singh N, Moody AR, Rochon-Terry G, Kiss A, Zavodni A. Identifying a high risk cardiovascular phenotype by carotid MRI-depicted intraplaque hemorrhage. The international journal of cardiovascular imaging 2013;29(7):1477-1483.

26. Noguchi T, Yamada N, Higashi M, Goto Y, Naito H. High-intensity signals in carotid plaques on T1-weighted magnetic resonance imaging predict coronary events in patients with coronary artery disease. Journal of the American College of Cardiology 2011;58(4):416-422.