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Contemporary Carotid Imaging and Approach to Treatment: Course Notes
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A. Objectives

1. To understand the current imaging modalities used for the diagnosis of symptomatic carotid atherosclerotic disease. The advantages and disadvantages of each and how they influence treatment decisions will be discussed.
2. To understand the definition and diagnosis of "vulnerable" atherosclerotic plaque and how this influences treatment decisions in asymptomatic patients with carotid stenosis.
3. To recognize the common cervical carotid and vertebral artery abnormalities in stroke, including stenosis, ulceration, intraluminal thrombus, near-occlusion and dissection on CT angiography (CTA) and MR angiography (MRA) studies.

A. Background

- Since the publication of NASCET in 1991, the method used in this study has been adopted as the gold standard for measurement of carotid stenosis. The decision to perform carotid endarterectomy (CEA) for symptomatic carotid atherosclerosis depended on luminal diameter and the stenosis severity. Luminal diameter/percentage stenosis remains the most utilized parameter determining the need for intervention.
- Although dated, it is instructive to review a few facts from this landmark study: all patients were symptomatic; all measurements of carotid stenosis were based on catheter angiography (now digital subtraction angiography, DSA); the benefit of CEA for those with >70% stenosis had a relative risk reduction of stroke or death of more than 80% compared to medical treatment; finer divisions of severe stenosis degree correlated with degrees of risk reduction after CEA (i.e. the worse the stenosis, the more the benefit from surgery); the complication rate (major stroke or death) of NASCET surgeons was 2.1%.
- This study therefore established: the importance of carotid stenosis measurement for surgical intervention to prevent stroke in symptomatic patients; the need for a standardized measurement method; the emphasis on surgically treating only symptomatic patients and; and the need for low surgical complication rates.
- Since 1991: the rapid development of carotid angioplasty and stenting (CAS); the inclusion of asymptomatic patients in surgical treatment paradigms; and the proliferation and technological advances of imaging modalities have

greatly expanded and perhaps complicated the diagnosis and treatment options for carotid atherosclerosis.
- Contemporary, less invasive carotid imaging techniques, including ultrasound (US), CTA and MRI with MRA have rendered DSA obsolete for diagnosis of carotid stenosis, and allowed unprecedented characterization of carotid plaque components. The concept and identification of complex, "vulnerable" plaque rather than merely stenosis severity is becoming important for treatment decisions.
- This course will review the capabilities of current imaging modalities for the diagnosis and characterization of carotid stenosis in both symptomatic and asymptomatic patients, and how this information can influence treatment decisions.

B. The Symptomatic Patient

1. Duplex Carotid Ultrasound (DUS)

- Still the most commonly used screening procedure, although reliability and reproducibility between labs restricts it to a screening rather than definitive role in decision-making.
- B-mode images are often excellent, can measure the stenosis, identify ulcers and intraluminal thrombus; 3D techniques can determine internal components of "vulnerable" carotid plaque.
- Doppler data, particularly peak systolic velocity (PSV) and ICA/CCA velocity ratios are currently the most valuable parameters for intervention.

2. CT Angiography (CTA)

- Now firmly established as the definitive diagnostic tool in cerebrovascular atherosclerosis (stroke/TIA)
- Fast, reliable, gives all the relevant extra-and intracranial vascular information, both anatomic and physiologic with 3-phase MIP images for intracranial collaterals and CT perfusion for ischemic penumbra
- Stenosis measurement: Can use NASCET method or absolute luminal diameter (1.3 mm).
- Intraluminal thrombus, ulceration, dissection all visible.
- Pitfalls: Calcification- importance of axial images; near occlusion (NO).
- Near-occlusion: defined as a very tight atherosclerotic stenosis in which the artery beyond is collapsed. There can be NO with or without full collapse. Full collapse shows a distal thread-like lumen or "string" sign and by definition represents > 99% stenosis by NASCET criteria. NO without full-collapse shows decreased caliber of the distal cervical ICA, but a more normal appearance. By definition, this represents > 95% stenosis by NASCET criteria. Important to recognize both conditions, because the standard NASCET method cannot be used!

- NO without full collapse has been under-recognized, multiple terminologies used, most commonly called "approaching near occlusion". Can be simulated by an unbalanced Circle of Willis, intracranial of proximal CCA stenosis.
- NO can be challenging to diagnose with DUS and MRI due to the small vessel lumen and complex, turbulent flow patterns.
- Evolving role for CTA in diagnosis of "vulnerable" plaque.

3. Plaque morphology (the PLAC Scale) on CTA: Predicting long-term anatomical success of Primary Carotid Stenting (PCS)

- CEA vs. CAS has been evaluated by multiple studies, with CREST widely interpreted as establishing equivalence despite higher risk of stroke with CAS
- Balloon angioplasty, pre- and post-stent implantation, is strongly associated with DWI lesions on post-procedural MRI.
- Embolic protection devices (EPDs) do not capture all emboli, are expensive and can be challenging to use.
- Primary carotid stenting (PCS) avoids intentional use of balloons and EPDs, and can be faster, less expensive, as effective and safe as standard techniques.
- Predicting Long-term outcome with Angioplasty of the Carotid artery (PLAC) scale uses plaque calcification (grades 0-4) and presence or absence of "soft", non-calcified plaque (A or B) to predict efficacy of PCS.
- Low-calcification grade, less thick calcification and moderate amounts of soft plaque are all associated with good long-term anatomic results (up to 30 months)
- In our practice, lesions with soft-plaque (A) and low calcification score (0-2) are candidates for PCS. Those with little soft-plaque (B) and higher calcification scores will require angioplasty balloons and EPDs for CAS, or are considered for CEA.

4. MR and MRA

- Value as a screening technique for carotid stenosis is limited, due to vulnerability of routine time-of-flight (TOF) and phase-contrast (PC) sequences to motion and flow artifacts, and the relatively low special resolution compared to CTA.
- Even with contrast-enhanced techniques (CEMRA), measurement can be challenging.
- Difficult to definitively diagnose complete occlusions, NO with and without full collapse.
- Limited availability in acute stroke/TIA setting, but DWI sequence can influence treatment decisions.
- Acute carotid/vertebral artery dissections: axial FSE T1 sequence still valuable for intramural thrombus.

C. The Asymptomatic Patient

1. Background

- Over 90% of carotid interventions in the US are in asymptomatic patients
- There are currently multiple clinical trials evaluating CEA, CAS and optimal medical therapy (OMT) in these patients.
- ACT 1 (published in 2016), CREST 2, SPACE 2, ECST 2, ACST 2
- There are controversies regarding annual stroke risk with contemporary OMT (statins), may be 1% or less.
- These developments have led to the concept of "vulnerable" plaque to identify those asymptomatic patients who are at increased risk of stroke/TIA and may benefit from pre-emptive CEA or CAS.
- Paradigm is shifting away from mere luminal diameter measurements to detailed characterization of plaque content using advanced imaging techniques.

2. The "Vulnerable" Plaque

- The key features of atherosclerotic plaque that predispose to rupture and distal emboli are the lipid-rich necrotic core (LRNC), intraplaque hemorrhage (IPH) and thin/ruptured fibrous cap (TRFC).
- All have been associated with stroke in lesser degrees of luminal stenosis (<50%)
- American Heart Association (AHA) MRI classification, Type VI (complex plaque with possible surface defect, hemorrhage or thrombus) strongly associated with stroke risk.
- Presence of IPH may result in up to 45% annual stroke risk in patients with > 50% stenosis.

3. Ultrasound (DUS and TCD)

- 5 categories of plaque morphology have been described on B-mode ultrasound. Those that are echolucent with heterogeneous content and irregular surface are considered to be unstable.
- 3 or more ulcers can predict future stroke risk (18% over 3yrs.).
- 3D techniques allow measurement of total plaque area and volume; can follow plaque progression and response to medical therapy.
- When combined with transcranial Doppler (TCD) detection of microembolic signals (MES), 2 or more/hr., found to be predictive of future stroke/TIA (15.6% annual risk).
- Contrast enhancement with microbubbles can detect angiogenesis, neovascularization and inflammation, all associated with risk of future stroke.

- Pitfalls: not good at differentiating IPH from LRNC, calcification obscures plaque contents, accuracy for detection of ulceration decreases with increasing stenosis severity.

4. CT/CTA

- Calcification often obscures detailed analysis of underlying plaque, variations in scanning parameters limits use of Hounsfield units (HU) to differentiate plaque components. Dual energy techniques can be used to improve plaque analysis.
- Main use is differentiation of "hard" from "soft" plaque, presence or absence of ulceration and intraluminal thrombus.
- "Soft" plaque contains fibrous tissue, lipids, thrombus and hemorrhage, but CT cannot reliably differentiate them or identify TRFC.
- Some relationship between thickness of "soft" plaque and AHA Type VI vulnerable plaque.
- "Rim" sign of adventitial calcification with internal soft plaque can be associated with IPH
- Plaque ulceration associated with increased lipid volume and worse stenosis
- Calcification may be a marker of adventitial neovascularity and propensity for IPH
- Plaque enhancement (increased HU) associated with neovascularity/inflammation and increased stroke risk.
- Evidence for CT risk assessment in asymptomatic patients is generally weak.

5. MRI/MRA

- Most widely studied and useful technique for plaque analysis and prediction of future stroke risk.
- AHA classification based on MRI, can reliably identify Type VI plaque, even in low-grade stenosis.
- IPH is most common feature of Type VI plaque, followed by TRFC and LRNC.
- MRI best for monitoring plaque progression and response to medical therapies.
- Contrast-enhanced techniques can show plaque enhancement, neovascularity
- Routine TOF and PC techniques as reliable as CT for detection of ulcers, accuracy improved with CEMRA
- Pitfalls: accessibility, 3T better than 1.5T, claustrophobia, motion artifact, safety issues (metal, pacemakers), gadolinium side-effects, specialized sequences using surface coils can take up 30 minutes.
- Dedicated T1 weighed sequences with fat suppression to detect IPH can be done in 5-6 minutes.
- Not yet practical as a screening technique

6. PET

- 18F-Fluorodeoxyglucose can identify inflammation in carotid plaque
- Research technique

D. <u>Summary</u>

- *In symptomatic patients:* CTA is the most accessible, informative and reliable diagnostic modality for cerebrovascular atherosclerosis
- DUS is the most accessible screening modality. TOF and PC MR are less accessible and reliable, CEMRA is more accurate
- Plaque analysis by CTA in symptomatic patients (the PLAC scale) can help determine CEA vs. CAS, whether PCS is appropriate.
- Plaque analysis by MRI and US is of limited clinical value. There is some evidence that CAS in patients with unstable plaque (i.e. IPH, TRFC, ulcerations) may be at greater risk of distal emboli with CAS. CEA, in which distal ICA is clamped, may be more appropriate.
- *In asymptomatic patients:* CTA is still the best technique for determination of luminal stenosis. The concept of "vulnerable" or unstable plaque is however becoming much more important to guide therapy. Identification of IPH, LRNC, TRFC, neovascularity and inflammation are important markers of future stroke risk. MRI (AHA classification) is the most accurate. US with TCD detection of MES very useful for prediction of future events. CT is currently of limited value for plaque characterization.

E. <u>Selected References</u>

1. Fox, Allan J. How to Measure Carotid Stenosis. Radiology 1993; 186: 316-318
2. Bartlett ES, Walters TD, Symons SP, Fox AJ. Quantification of carotid stenosis on CT angiography. AJNR Am J Neuroradiol 2006; 27(1): 13-19.
3. Johansson E and Fox AJ. Carotid Near-Occlusion: A Comprehensive Review, Part 1-Definition, Terminology and Diagnosis. AJNR Am J Neuroradiol 2016; 37(1): 2-10
4. Johansson E and Fox AJ. Carotid Near-Occlusion: A Comprehensive Review, Part 2 – Prognosis and Treatment, Pathophysiology, Confusions, and Areas for Improvement. AJNR Am J Neuroradiol 2016; 37(2): 200-204
5. Pelz DM, Lownie SP, Lee DH, Boulton MR. Plaque morphology (the PLAC Scale) on CT angiography: predicting long-term anatomical success of primary carotid stenting. J Neurosurg 2015; 123(4): 856-861.
6. Cai JM, Hatsukami TS, Ferguson MS et al. Classification of Human Carotid Atherosclerotic Lesions With In Vivo Multicontrast Magnetic Resonance Imaging. Circulation 2002; 106: 1368-1373
7. Gupta A, Baradaran H, Schweitzer AD et al. Carotid Plaque MRI and Stroke Risk. A Systematic Review and Meta-analysis. Stroke 2013; 44: 3071-3077
8. Gupta A, Mushlin AI, Kamel H. Cost-effectiveness of Carotid Plaque MR Imaging as a Stroke Risk Stratification Tool in Asymptomatic Carotid Artery Stenosis. Radiology 2015; 277 (3): 763-771

9. Yuan J, Usman A, Das T et al. Imaging Carotid Atherosclerotic Plaque Ulceration: Comparison of Advanced Imaging Modalities and Recent Developments. AJNR Am J Neuroradiol 2017; 38 (4): 664-71
10. Eisenmenger LB, Aldred BW, Kim S-E et al. Prediction of Carotid Intraplaque Hemorrhage Using Adventitial Calcification and Plaque Thickness on CTA. AJNR Am J Neuroradiol 2016; 37: 1496-1503
11. Doonan RJ, Gorgui J, Veinot JP et al. Plaque echodensity and textural features are associated with histologic carotid plaque instability. J Vasc Surg 2016; 64: 671-7
12. Demarco JK (ed). Plaque Imaging. Neuroimaging Clinics of North America February 2016; 26 (1).