Atherosclerotic Peripheral Vascular Disease Symposium II: Vascular Magnetic Resonance and Computed Tomographic Imaging

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Circulation 2008;118;2837-2844
DOI: 10.1161/CIRCULATIONAHA.108.191173
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

Atherosclerotic Peripheral Vascular Disease Symposium II

Vascular Magnetic Resonance and Computed Tomographic Imaging

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Over the past 10 years, there has been a rapid adoption of new technology that has allowed us to image the vascular system in a noninvasive manner with greater speed and improved resolution. The "gold standard," catheter-based angiography, is now more often used with therapeutic interventions rather than purely diagnostic studies. Catheter-based angiography is being replaced by computerized tomographic angiography (CTA) and magnetic resonance angiography (MRA) for carotid, renal, and peripheral vascular diagnostic examinations. The goal of this writing group is to review the evidence-based approach to selection of imaging modalities; however, regional availability and expertise are recognized as important factors in the selection of imaging modalities.

Technical Overview: CTA

The advent of multidetector-row computed tomographic (MDCT) scanners has allowed us to obtain excellent images of the vascular tree from the head to the toes. Initial studies performed on a single-row scanner cannot compare to those obtained with scanners with 4 rows or more. Rubin et al[1] showed in their initial feasibility study of CTA of the aortoiliac system that there was no advantage to a single-row scanner over an MDCT scanner. The capabilities of MDCT have evolved substantially since that original report was published in 2000, and a large number of 64-row scanners are now in use across the United States. CTA allows acquisition of high-resolution volumetric data sets that can be viewed in multiple planes and with a variety of visualization techniques (Figure 1). The additional detector rows allow for greater speed of scanning so that longitudinal coverage can be increased, while at the same time, near-isotropic voxels can be maintained. Compared with catheter-based angiography and MRA, CTA is faster and more comfortable for patients, although it has been suggested that the interpretation time may be longer than for the other imaging modalities.[2] Physicians should be able to review these data in more than the standard transverse plane, because multiplanar reformations, curved planar reformations perpendicular to the median arterial centerline,[3] volume rendering, and maximum-intensity projections all have different advantages and disadvantages.[4] Important nonvascular findings are not uncommon in the population being evaluated for vascular disease because patients often have multiple risk factors, such as smoking and advanced age. Nearly half of the patients undergoing CTA for vascular disease had unsuspected findings that were clinically insignificant, but 5% had life-threatening pathology, such as unsuspected malignancies.[5]

Advantages of CTA over MRA include better patient acceptance, speed of examination, better spatial resolution, and the ability to evaluate previously stented arteries.[6] Disadvantages of CTA include image interference from calcified arteries and the need for potentially nephrotoxic contrast and radiation exposure. Willmann et al[7] showed the mean effective radiation dose for a lower-extremity CTA performed on a 16-detector row scanner with online tube-current modulation was 4-fold lower for men and 5-fold lower for women than with digital subtraction angiography (DSA). Radiation dosing to the female breast ranges from 1 to 6 cGy with typical body computed tomography (CT) protocols on a 16-detector-row scanner.[8] The late effects of radiation exposure are more important in younger patients; however; physicians should be aware of this issue and strive to keep dosing as low as reasonably possible.

CT Contrast Agents

Iodinated contrast agents used in CT are known to increase risk for contrast-induced nephropathy (CIN). This is defined in most cases as an increase in serum creatinine level >25%

The Executive Summary and other writing group reports for these proceedings are available online at http://circ.ahajournals.org (*Circulation*. 2008;118:2811–2825; 2826–2829; 2830–2836; 2845–2851; 2852–2859; 2860–2863; 2864–2872; and 2873–2878).

These proceedings were approved by the American Heart Association Science Advisory and Coordinating Committee on June 2, 2008. A copy of these proceedings is available at http://www.americanheart.org/presenter.jhtml?identifier=3003999 by selecting either the "topic list" link or the "chronological list" link (No. LS-1882). To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

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(*Circulation*. 2008;118:2837-2844.)

***Circulation* is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.108.191173**

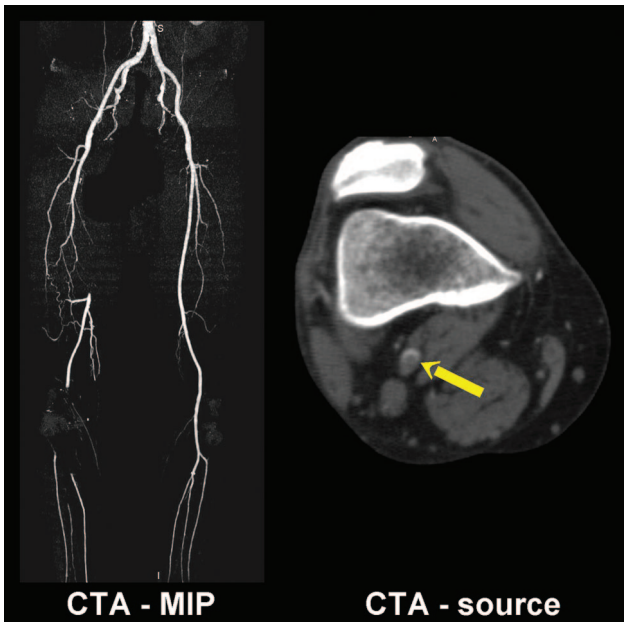

Figure 1. Maximum-intensity projection (MIP) image of a standard runoff CTA performed on a 64-detector-row CT scanner. Note occlusion of superficial femoral artery with reconstitution of a blind segment of popliteal artery and occlusion of the proximal trifurcation arteries. Axial source image from below the knee (right panel). Note the meniscus of contrast (arrow) at the right popliteal artery indicating acute thrombus or embolus.

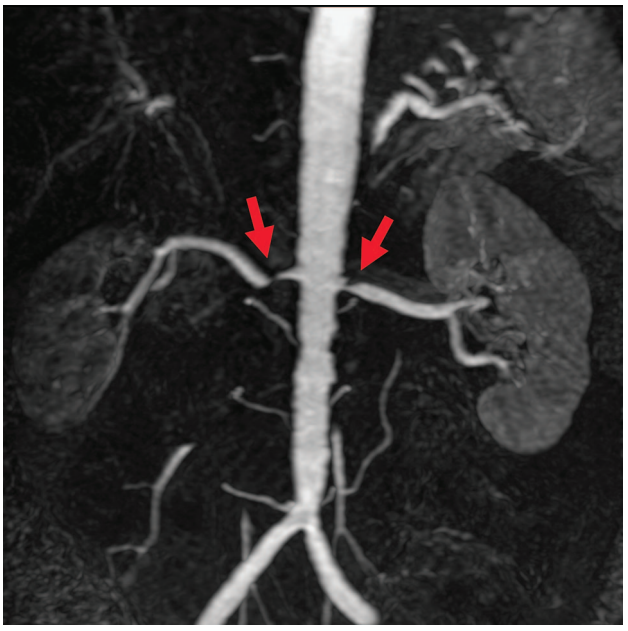

Figure 2. Gadolinium contrast–enhanced dynamic TRICKS (time-resolved imaging of contrast kinetics) MRA shows severe stenosis of the renal arteries bilaterally (arrows). Case courtesy of Scott Reeder, MD, PhD.

or >0.5 mg/dL above baseline that occurs within 3 days of contrast administration in the absence of other causes. Patients who are considered at highest risk are those with baseline renal insufficiency, especially those with concomitant diabetes mellitus, in whom the risk of CIN after catheter-based angiography may be as high as 25%.[9] Other risk factors for CIN include multiple myeloma, proteinuria, concomitant nephrotoxic drug use, hypertension, congestive heart failure, hyperuricemia, and dehydration. Contrast-specific factors such as volume of contrast and type of contrast also play a role in risk of CIN. High-osmolar contrast puts patients with preexisting renal impairment at twice the risk of developing CIN as low-osmolar contrast.[10] Some recent reports have indicated that iodixanol, an isosmolar nonionic dimer, may be less nephrotoxic than other low-osmolar contrast material[11]; however, others have countered this statement, showing no statistically significant difference in rates of CIN between the 2 agents.[12] Spinazzi and Pozzi Mucelli[13] reviewed the available literature and concluded that all patients with preexisting renal insufficiency were at higher risk for CIN, no matter what type of contrast was used. All physicians using contrast material should be aware of the associated risks, and facilities are encouraged to have general screening programs to identify patients at high risk for CIN so that procedures can be modified for patient safety.

Technical Overview: MRA

Just as with CTA, rapid advances in MRA technology in the past several years have led to improvements in resolution, anatomic coverage, and speed of image acquisition.[14–19] The lack of radiation exposure and the noninvasive nature of MRA offer advantages over CT in many settings.[20] Traditional MRA techniques include both multislice (2-dimensional) and volumetric (3-dimensionsal) time-of-flight techniques. These have shown excellent utility in carotid and intracranial applications. However, most carotid, body, and peripheral MRA is currently performed with gadolinium-enhanced sequences to improve examination speed, anatomic coverage, and small-vessel resolution. Intravenous injection of gadolinium shortens the T1 relaxation time of blood, which leads to a transiently higher intravascular signal that can be captured with proper MRA sequence timing. Newer time-resolved gadolinium-enhanced sequences, such as time-resolved imaging of contrast kinetics (TRICKS), produce an additional "angiographic" MRA series of dynamic arteriovenous contrast passage, showing both vascular anatomy and functional effects of stenoses, such as delayed filling of distal vascular territories[21] (Figure 2). Carotid evaluations can be imaged effectively with noncontrast time-of-flight MRA sequences, but peripheral and body applications usually dictate the use of more advanced or specialized protocols that use dynamic gadolinium-injection techniques. Specific MRA protocols may also take advantage of moving-table techniques or multiarray, parallel-imaging hardware and software to optimize large-field-of-view imaging.

Magnetic Resonance Contrast Agents

Gadolinium-based contrast agents have long been touted as non-nephrotoxic. Their use, therefore, has been extended to patients undergoing DSA and CTA.[22–24] Very recently, however, the safety of gadolinium in patients with severe renal insufficiency has come into question, in terms of both renal toxicity and potential systemic illness. The US Food and Drug Administration (FDA) has issued a warning on the use of gadolinium in patients with renal impairment because it

has been linked to the development of nephrogenic systemic fibrosis, also known as nephrogenic fibrosing dermopathy.[25] Nephrogenic systemic fibrosis is the preferred term because it indicates the widespread systemic effect that this disease may show. Nephrogenic systemic fibrosis is still considered rare, with only 90 cases reported to the FDA at the time of the advisory warning; however, it can be severely debilitating and has been linked to patient death due to respiratory compromise from diaphragmatic and cardiac involvement. The FDA recommends that physicians halt non–FDA–approved use of gadolinium, including catheter-based angiography and MRA, on patients with severe renal impairment. Although the exact cause of nephrogenic systemic fibrosis has yet to be proven, tighter magnetic resonance imaging (MRI) screening procedures are now recommended before gadolinium use is considered in patients with any degree of renal insufficiency.[26] Patients with severe renal insufficiency, including those with stage 3 to 4 chronic renal insufficiency, should receive hemodialysis as soon as possible after the administration of gadolinium chelates.

Multiple additional reports have been published about the development of acute renal failure in patients receiving high doses of gadolinium chelates (>0.3 mmol/kg), which is a fairly typical dose for lower-extremity MRA examinations.[27,28] The patients most at risk are those with diabetic nephropathy and low glomerular filtration rate.[29] The greatest benefit of MRA compared with CTA in the recent past was the use of non-nephrotoxic agents in imaging patients at high risk for iodinated CIN. That presumed benefit might no longer hold true. Physicians should be aware that there are potential nephrotoxic and systemic risks with the use of high-dose gadolinium chelates and should exercise caution in high-risk patients.

Clinical Applications

Carotid Bifurcation

Large trials such as the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) have shown that a carotid bifurcation stenosis of ≥70% in symptomatic patients should be treated to reduce the risk of stroke.[30,31] Cerebral angiography has been touted as the diagnostic standard on which carotid artery interventions should be based. Cerebral angiography, however, carries a risk of stroke of ≈1.3%.[32] Duplex ultrasound is a well-validated screening tool for the presence of carotid artery stenosis; however, it can be operator and patient dependent, so results are often confirmed by additional testing before treatment. Initially, this was performed with an unenhanced time-of-flight MRA. Currently, the additional testing is more often gadolinium-enhanced MRA, although CTA is increasingly being used.

A recent meta-analysis was performed comparing methods of noninvasive carotid imaging with contrast angiography serving as the diagnostic reference standard. Gadolinium-enhanced MRA was found to be the most sensitive at 95% (95% CI, 88% to 97%) and specific at 93% (95% CI, 89% to 96%) for stenoses >70%, compared with standard MRA and CTA, which had a sensitivity of 89% (95% CI, 88% to 76%) and specificity of 84% (95% CI, 84% to 94%). CTA is a new technique for the evaluation of carotid disease, but it can be limited in up to 6% of patients because of artifacts from dental implants and swallowing.[33] Multidetector CTA has been found to have a high sensitivity (nearly 100%) for detecting >70% stenosis and a high negative predictive value, although it may slightly overestimate the degree of stenosis.[34] CTA of the carotid bifurcation is being advocated as an important tool in the initial evaluation of patients being imaged for acute stroke (Figures 3 and 4).

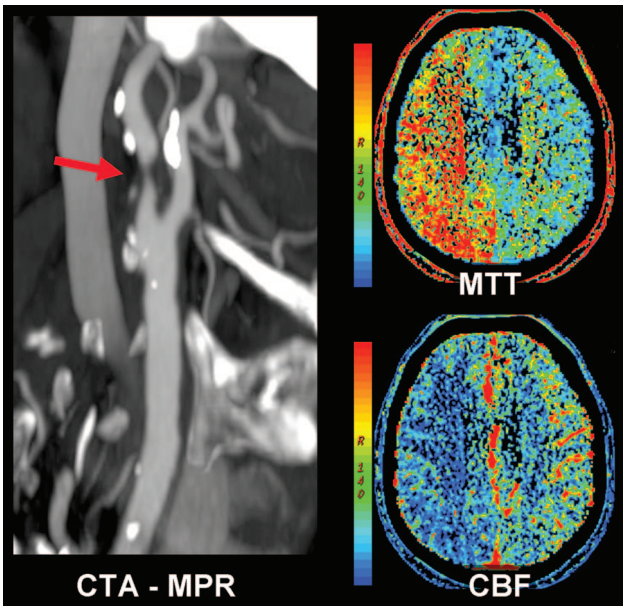

Figure 3. CTA and CT perfusion in severe internal carotid artery stenosis. Multiplanar reformations (MPR) show an 85% diameter stenosis and mural calcifications at the internal carotid artery origin (arrow), accompanied by severe prolongation in perfusion mean transit time (MTT) and reduction in cerebral blood flow (CBF).

Acute Stroke Imaging

The field of stroke imaging is changing rapidly because of both technical and conceptual advances. CT and MRI now go beyond brain structural analysis to allow a comprehensive, physiological assessment of stroke and its causes. A key concept derived from recent ischemic stroke imaging studies is the idea that CT and magnetic resonance can rapidly define both the "core" of the infarcted tissue and the surrounding tissue at risk, or the "penumbra."[35] Most acute stroke patients seen within several hours will have a variable amount of penumbra, tissue that is injured but potentially can be salvaged with timely reperfusion or other therapy. The penumbra is therefore the target for acute stroke intervention (Figure 5). Both the core and penumbra can be defined operationally with noninvasive CT and magnetic resonance studies that include perfusion imaging.[36–38] Perfusion examinations use a series of rapidly acquired CT or magnetic resonance images shot repeatedly in serial fashion during the wash-in and washout phases of an intravenous contrast bolus. Postprocessing algorithms create maps of the key blood-delivery perfusion parameters, including mean transit time, cerebral blood volume, and cerebral blood flow. Very low

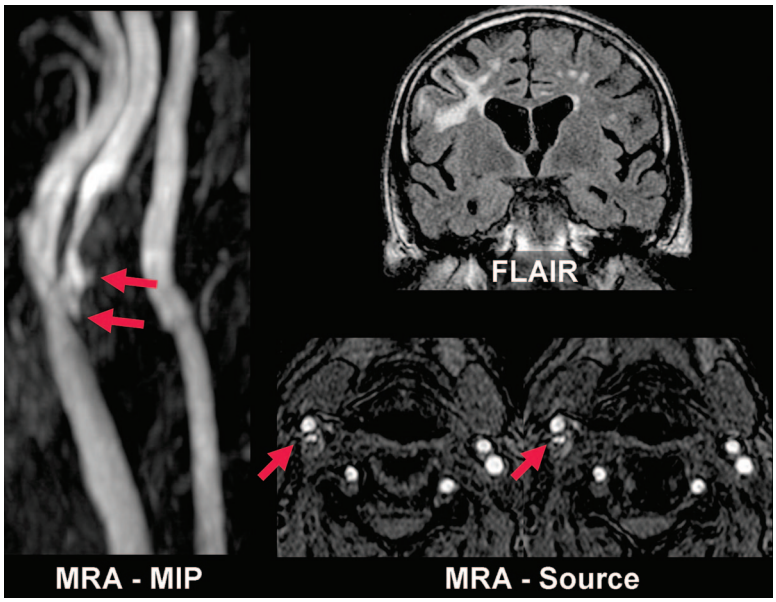

Figure 4. Noncontrast 3-dimensional time-of-flight MRA in right carotid atherosclerosis. The degree of narrowing is only 70% by NASCET criteria, but there are also signs of plaque ulceration (arrows) and deep carotid watershed distribution ischemic changes on coronal FLAIR (fluid-attenuated inversion recovery) images. MIP indicates maximum-intensity projection.

blood volumes suggest uncompensated areas of core infarction, whereas surrounding areas with prolonged transit times and reduced blood flow represent a "worst-case" estimate of penumbra. With MRI, diffusion-weighted imaging is able to very sensitively detect ischemic changes within minutes of stroke onset much better than noncontrast CT; however, perfusion imaging is needed to determine whether there is tissue at risk beyond the early infarct core—that is, an ischemic penumbra. When the parenchymal core alongside the surrounding penumbra is reviewed, a "mismatch" of ischemic tissue can be seen and rationally targeted for treatment. Although there is much debate about the exact combination of parameters that best defines core and penumbra, the concept of mismatch imaging is rapidly gaining acceptance.[39]

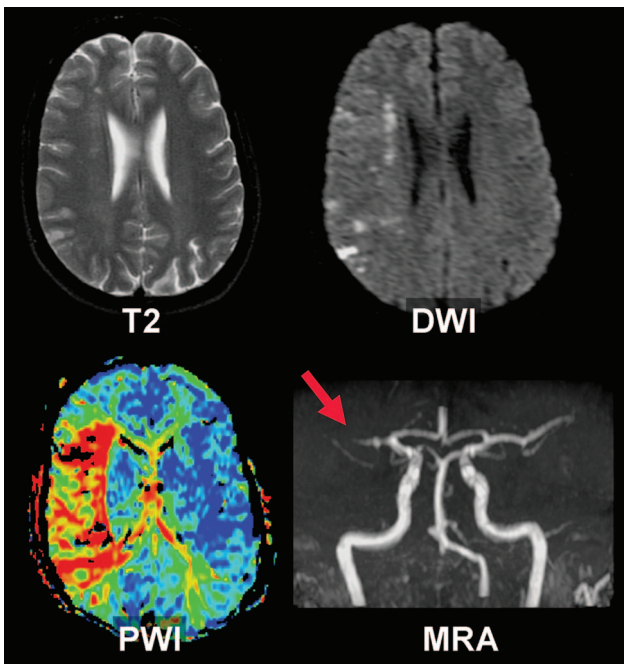

Figure 5. Acute right middle cerebral artery occlusion and ischemia. Noncontrast 3-dimensional time-of-flight MRA shows no flow beyond the M1 segment of the middle cerebral artery (arrow). There are early ischemic changes in a small portion of the right hemisphere on diffusion-weighted images (DWI) and a larger area of impaired perfusion on perfusion-weighted images (PWI; first moment transit time). Such a PWI–DWI mismatch may help define a target for emergent revascularization.

Perfusion–diffusion mismatch has now been used successfully in 2 separate phase 2 studies of thrombolysis beyond 3 hours, and several more trials have just ended or will be completed soon.[40] The Desmoteplase in Acute Ischemic Stroke (DIAS) and Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DEDAS) trials used intravenous desmoteplase with a 9-hour time window, with selection made by perfusion-weighted imaging/diffusion-weighted imaging mismatch.[41,42] Recanalization at optimal dose tiers was ≈60%, low hemorrhage rates were observed, and favorable outcomes were seen at 90 days with this approach. The Diffusion and perfusion imaging Evaluation For Understanding Stroke Evolution (DEFUSE) investigators have reported similar positive results for intravenous tissue plasminogen activator at 6 hours with the use of perfusion–diffusion mismatch selection.[43] Additional support for the concept of advanced MRI selection for therapy comes from recently reported large, open-label tissue plasminogen activator series that show safety results and outcomes with perfusion-weighted imaging/diffusion-weighted imaging selection at 3 to 6 hours that are equal to or better than with plain CT selection at 0 to 3 hours.[44,45]

The same new, rapid CT and magnetic resonance scanners that allow perfusion assessment also yield high-quality noninvasive imaging for the arteries and veins ultimately responsible for stroke. With variation according to the application and exact technique, both CTA and MRA yield sensitivities and specificities on the order of 85% to 95% for common stroke-related applications.[19,46–50] Neither MRA nor CTA has proved effective at plaque characterization, but research in this field is ongoing.

Renal Artery Disease

The prevalence of renovascular disease in the hypertensive population varies from 1% to 5%.[51,52] The prevalence may be as high as 15% to 40%, however, in populations considered at risk, such as those with underlying coronary artery disease[53] or peripheral artery disease.[54] Duplex ultrasound is a good technique for evaluation of renal artery stenosis, but it is limited by operator experience, patient cooperation, and body habitus, which limit its universal use. Renal CTA and MRA have therefore come to the forefront for noninvasive imaging when renal artery stenosis is suspected clinically.

A meta-analysis conducted by Vasbinder et al[55] concluded that CTA had a range of sensitivity of 94% to 100% and a specificity of 92% to 99% for significant renal artery stenosis. Contrast-enhanced MRA had a similar result, with sensitivity ranging from 88% to 100% and specificity of 75% to 100%. These comparisons were based on data from a single-row-detector spiral CT scanner and standard gadolinium-enhanced MRA techniques. In the largest prospective trial to date published by the Dutch (the RADISH trial [Renal Artery Diagnostic Imaging Study in Hypertension]), 356 patients suspected of renal vascular hypertension were evaluated with CTA, MRA, and DSA, with the latter used as the reference standard.[56] They found that in their population with an overall prevalence of renal artery stenosis of 20%, CTA had an overall sensitivity of only 64%, with a specificity of 92%. Gadolinium-enhanced MRA faired slightly worse, with a sensitivity of 62% and a specificity of 84%. Another disturbing finding in RADISH was in the subgroup analysis on patients with fibromuscular disease, in which sensitivities were only 28% and 22%, respectively, for CTA and MRA, although both had a high specificity for the disease. This study led the authors to conclude that neither CTA nor MRA was accurate enough to replace DSA in the evaluation of patients with suspected renovascular hypertension.

An important limitation of the technique of the CTAs performed during the RADISH study is that the majority of the studies were performed with a single-detector-row helical CT scanner. Only 21 of the 356 studies were performed on an MDCT scanner (4 rows). All but these 21 patients were scanned at 2.5- to 3.0-mm collimation, which is too thick for optimal renal arterial assessment. MDCT scans of the renal arteries should be performed with 0.5- to 1.25-mm section thickness and should be reconstructed with overlapping sections. Moreover, the prevalence of fibromuscular dysplasia in this study population was atypically high as compared with most randomized populations of patients with renovascular hypertension, which further biased the results. A limited number of published studies to date have used more current MDCT for renal artery stenosis. One small study evaluated 50 patients with suspected renovascular hypertension by using both MDCT and DSA. That study found sensitivity, specificity, and accuracy of MDCT of 100%, 98.6%, and 96.9%, respectively.[57] Common postprocessing tools were used in the RADISH study, although a specific protocol was not provided. It is suspected that this was likely based on the interpretation of maximum-intensity projection images with reference to the cross-sectional data. It has been demonstrated previously that reliance on maximum-intensity projection images alone is insufficient and that maximum sensitivity is gained through the use of multiple image reconstructions, specifically with quantitative measurements of the luminal diameter.[58] Many workstations now have segmentation programs available in which the user can establish orthogonal planes through the vessel, with quantitative vessel measurements performed automatically. This feature likely will reduce the variability introduced by differences in window and level settings, as well as user selection of placement of calipers for measurements.

Contrast-enhanced MRA is now the accepted standard of vascular imaging outside the brain, rather than noncontrast, time-of-flight imaging. MDCT angiography has better spatial resolution than MRA, but newer MRA techniques that use sense-encoding and parallel-acquisition techniques have allowed a reduction in section thickness to $\leq$1.5 mm. Studies comparing MDCTA and MRA have shown them to be equally sensitive and specific for the detection of renal artery stenosis. Not unexpectedly, however, patient acceptance of CTA is higher than for MRA or DSA.[2] A note of caution should be made with regard to patients with suspected fibromuscular disease. The lower spatial resolution of MRA, especially at 3-mm section thickness, may not be sensitive enough to detect the subtle changes of fibromuscular disease. There are no studies to date on MRA evaluation of this entity other than the subgroup report from the RADISH trial, in which the sensitivity was only 22%. The only other published report on CTA for fibromuscular disease was from Beregi et al,[59] who used a single-detector scanner in patients with known fibromuscular disease. They demonstrated a sensitivity of 87% by utilizing cross-sectional, transverse imaging, and maximum-intensity projections.

CTA is advantageous over MRA for assessment of renal arteries after stent placement.[6] Susceptibility artifact from metal from most stents does not allow assessment of the inner lumen, whereas CT imaging is usually not affected to the same degree. Overall, most institutions should choose CTA or MRA on the basis of local availability and expertise, as well as patient-dependent factors such as preexisting renal impairment.

Peripheral Artery Disease

Patients with peripheral artery disease who have significant, lifestyle-altering claudication or critical limb ischemia require some form of diagnostic imaging for the purpose of treatment planning. In the not-too-distant past, the imaging study used was peripheral angiography. Currently, this invasive testing has been replaced almost completely by noninvasive imaging with CTA or MRA. The choice of study should be based on regional availability and expertise.

Rubin et al,[60] in the first published experience of 4-row MDCT angiography in the evaluation of peripheral artery disease patients, demonstrated the feasibility and robustness of the technique for imaging the entirety of the lower-extremity inflow and runoff. CTA was even able to visualize segments of arteries distal to occlusions that were not visible on routine DSA imaging. The technique of CTA may be even more robust with the introduction of 16- to 64-row scanners. Multiple published studies are available comparing 4-row

CTA with DSA, yielding a range of sensitivities from 89% to 99% and a range of specificities from 83% to 100%.[3,61–64] Sixteen-row systems allow isotropic, submillimeter imaging of the entire vascular tree. This means that although the images are acquired in the axial plane, with workstations, they can be viewed from any other plane without loss in spatial resolution. The use of submillimeter section thickness necessitates greater x-ray tube outputs to overcome the resulting noise than is required with thicker, 1-mm sections. To date, no data suggest improved characterization of peripheral artery disease with submillimeter section thickness compared with 1- to 1.5-mm section thickness. The added noise, particularly in larger patients, that results from this technique may limit its applicability. Willmann et al[7] published their experience with CTA in which a 16-detector-row CT scanner and 1.5-mm section thickness were used. Although the number of patients included was small, they found that CTA was diagnostic at all segments, with a sensitivity and a specificity of 96% and 97%, respectively.

Gadolinium-enhanced 3-dimensional MRA examinations can be performed with a bolus chase (moving-table) sequence, which allows improved visualization of the peripheral arteries. The abdominal aorta and superficial femoral segments are imaged reliably with this technique. Problems can arise, however, with imaging of the infrapopliteal arterial segments. Venous contamination is a common problem in the infrapopliteal segment that can cause the images to be nondiagnostic in up to 43% of patients.[18] Multiple other techniques are being developed to help eliminate this problem, including integrated parallel acquisitions and hybrid studies with dedicated stations at the calf and foot. Hybrid MRA of the calf and foot may be able to detect target vessels for revascularization that are not visible on standard DSA.[65] Sensitivity encoding or parallel acquisition, either alone or in combination with dedicated peripheral phased-array coils, increases the speed of image acquisition of MRA so that the timing of imaging at the calf or the resolution of the imaging can be improved.[15] No single protocol has been accepted for universal use for MRA because most protocols are vendor specific.

Recommendations

Many areas are open for future research. The writing group has identified the following important topics:

- Intravascular device safety at high-field-strength MRI (3 Tesla and greater)
- Functional imaging for significant stenoses and clinical response to treatment
- Lowering CT radiation exposure with satisfactory image quality
- Plaque characterization, especially in the carotid arteries
- Prevention of CIN, including strategies to reduce the volume of contrast needed
- Means of identifying patients at risk for developing nephrogenic systemic fibrosis
- Rapid techniques for visualizing blood vessels on MRI that do not require the use of gadolinium-based contrast agents.

Disclosures

Potential conflicts of interest for members of the writing groups for all sections of these conference proceedings are provided in a disclosure table included with the Executive Summary, which is available online at http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.108.191170.

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KEY WORDS: AHA Conference Proceedings ■ cerebrovascular disorders ■ peripheral vascular disease ■ imaging ■ magnetic resonance imaging