Comparing Vessel Imaging

Noncontrast Computed Tomography/Computed Tomographic Angiography Should Be the New Minimum Standard in Acute Disabling Stroke

Andrew M. Demchuk, MD; Bijoy K. Menon, MD, MSc; Mayank Goyal, MD

The role of vascular imaging in the assessment of acute stroke has been debated for decades since the demonstration of intravenous tissue-type plasminogen activator (tPA) efficacy.\(^1\)\(^-\)\(^3\) It would seem logical that a disease involving the vasculature of the brain should require evaluation of that vasculature to best plan appropriate treatment. The major limitation to routine vessel imaging had been access to a modality that can provide this information noninvasively, accurately, and efficiently. Currently, there are 4 imaging modalities capable of providing vascular information in acute stroke. Given the high resource intensity and invasive nature of cerebral angiography, there is little place for this modality as a pure diagnostic tool in the acute stroke setting. The 3 noninvasive tests that could be used in acute stroke include computed tomographic (CT) angiography (CTA), magnetic resonance (MR) angiography (MRA), and transcranial Doppler (TCD)/transcranial color-coded sonography (TCCS)+carotid duplex sonography. This review will consider characteristics (Table 1) important for evaluating and comparing the 3 modalities as the diagnostic tool of choice for acute stroke assessment and treatment decision making. In the past, vascular imaging information did not significantly alter the evidence-based acute treatment plan, but this has now changed with new evidence for endovascular treatment renewing the debate on which should be the standard imaging approach be if a patient presents acutely (<6 hours from onset) with acute disabling stroke symptoms?

Methodology of the 3 Noninvasive Vascular Imaging Modalities

Each of the 3 modalities have different methods of acquisition but are all capable of imaging both the extracranial and intracranial arterial circulation. CTA is a CT technique that requires an injection of intravenous x-ray contrast in the arm with rapid movement of the CT gantry where x-ray information is gathered by a spiral or helical acquisition in 3-dimensional (3D) that starts usually at the aortic arch level and tracks the bolus through the neck and head for ≈6 s (for a single-phase CTA) to 20 to 25 s (for a multiphase CTA) when the arteries are maximally filled with contrast agent for excellent signal to noise.

MRA is a group of techniques based on magnetic resonance imaging (MRI) using different MRI techniques. Three-dimensional time of flight MRA does not require gadolinium contrast and is the preferred flow-dependent technique because of fast acquisition time and excellent spatial resolution for imaging of the intracranial arteries. Phase-contrast MRA is a technique that allows for blood flow measurements through encoding of velocity but has less spatial resolution than time of flight. For the extracranial arteries, cervical contrast-enhanced MRA using an intravenous injection of gadolinium contrast is more accurate and superior to noncontrast alternatives.

TCD is an ultrasound technique that flashlights ultrasound energy through 1 of the 4 bone windows through the skull to collect Doppler signals of arterial waveforms. TCCS uses high-resolution systems and sector transducers to enable visualization of the proximal intracranial arteries through intact skull by color coding of blood flow velocity. Angle correction of velocity is only possible with TCCS. Both TCD and TCCS are used in acute stroke for intracranial occlusion detection. Intracranial ultrasonography is complemented by extracranial ultrasound imaging by carotid duplex sonography. Carotid duplex sonography has limitations in extent of visualization, with limited evaluation of the distally internal carotid artery and much of the vertebral artery course.

Time Requirement for Image Acquisition and Interpretation

Each of the 3 noninvasive modalities introduce some measure of time delay to the acute stroke assessment process. This is important when one considers the clinical benefit of minimizing door-to-needle times when intravenous tPA is administered. Recent studies suggest a 3% to 4% absolute reduction in excellent outcomes with intravenous tPA for each hour delay in intravenous tPA initiation from stroke onset.\(^4\) Endovascular treatment is also time dependent with a 7% to 10% reduction in good outcomes and 2% to 4% increase in mortality per hour.

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delay to reperfusion. CTA can be time efficient when immediately performed after noncontrast CT (NCCT), usually adding only 2 to 5 minutes to CT table time. CTA information is not required for intravenous tPA decision making, and so it can be performed simultaneously while reconstituting the vial of intravenous tPA, drawing up the tPA bolus in a syringe and preparation of the intravenous tPA infusion pump tubing. tPA bolus administration and infusion can then be performed on the CT table immediately after CTA images have been acquired or even before the CTA in cases where there is a delay to CTA initiation. There should be no delay between tPA bolus administration and initiation of tPA infusion to optimize pharmacokinetics of tPA. MRA is burdened by more significant delays known to the MRI environment, such as metal screening, metal removal, and individual MR sequence acquisition, which can add up to a 20- to 50-minute delay in door-to-needle times compared with CT-based intravenous tPA treatment. TCD has the advantage of being a bedside tool that could be performed before NCCT. However, given limitations in quickly identifying the location of intracranial thrombus and lack of adequately trained transcranial sonographers, timely evaluation of the vasculature with TCD is not realistic at most centers.

Accessibility

All 3 modalities are available in most tertiary level centers. CTA is now possible at most community hospitals given the wide dissemination of multidetector CT systems that acquire multiple slices simultaneously to increase the speed of CT acquisition crucial to high-resolution CTA. CTA has seen a large increase in use during the past decade as a result of increased coverage. The typical radiation dose of a full stroke CT/CT-angio head/neck protocol using current CT systems is ≈7 to 9 mSv, which conforms to the 2012 International Commission on Radiological Protection guidelines (Table 2) and compares favorably with routinely performed single CT studies of the chest (7–11.3 mSv) and abdomen (8–11.7 mSv). The estimated lifetime risk of death from cancer attributable to a CT/CTA scan is estimated at 0.02% to 0.04%. CIN is defined as a 25% elevation from baseline of serum creatinine or an absolute increase of 0.5 mg/

> Table 1. Comparison of Vascular Imaging Techniques

<table>
<thead>
<tr>
<th>Feature</th>
<th>CTA</th>
<th>MRA</th>
<th>TCD/TCCD</th>
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<tbody>
<tr>
<td>Time requirement for acquisition and interpretation</td>
<td>3–5 min</td>
<td>With screening/preparing/imaging time: 30 min</td>
<td>10–30 min</td>
</tr>
<tr>
<td>Accessibility</td>
<td>CT technology in most hospitals, available 24×7, mostly near ED</td>
<td>Not available 24×7</td>
<td>Large operator dependence</td>
</tr>
<tr>
<td>Safety</td>
<td>Radiation risk low</td>
<td>No risk</td>
<td>No risk</td>
</tr>
<tr>
<td>ICH management</td>
<td>Secondary causes (aneurysm and AVM)</td>
<td>CTA spot sign</td>
<td></td>
</tr>
<tr>
<td>Occlusion detection</td>
<td>High accuracy proximally</td>
<td>Less accurate distally than CTA</td>
<td>Proximal occlusion only</td>
</tr>
<tr>
<td>Collateral assessment</td>
<td>Robust</td>
<td>Limited</td>
<td>No value</td>
</tr>
<tr>
<td>Great vessel/catheter access</td>
<td>Multiphase CTA captures delay</td>
<td>Dynamic MRA has potential</td>
<td>No value</td>
</tr>
<tr>
<td>Validation as selection tool in acute stroke RCTs</td>
<td>5 positive endovascular RCTs</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Potential as surrogate measure of treatment effect</td>
<td>Ideal tool for recanalization assessment</td>
<td>Cannot accurately assess distal vasculature</td>
<td>Yes</td>
</tr>
<tr>
<td>Emerging techniques</td>
<td>Dynamic CTA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multiphase CTA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AVM indicates arteriovenous malformation; CIN, contrast-induced nephropathy; CTA, computed tomographic angiography; ED, emergency department; ICH, intracerebral hemorrhage; MRA, magnetic resonance angiography; RCT, randomized controlled trial; TCD, transcranial Doppler; and TCCD, transcranial color Doppler.

Safety

TCD/transcranial color Doppler and MRA are both safe procedures with minimal risk especially without contrast administration. CTA has perceived safety concerns that include allergic reactions, additional radiation dose, and risk of contrast-induced nephropathy (CIN). Serious x-ray contrast reactions are rare, although occurring in 1 to 2 of 1000 and 1 to 2 of 10000 examinations with high and low osmolarity agents, respectively. Most cases occur immediately post injection and are quickly identified and addressed. In terms of radiation risk, intracranial CTA dose is not markedly different from NCCT unless CTA neck imaging is also performed (aortic arch to vertex is associated with a higher dose of 1–3 mSv because of the increased coverage). The estimated lifetime risk of death from cancer attributable to a CT/CTA scan is estimated at 0.02% to 0.04%. CIN is defined as a 25% elevation from baseline of serum creatinine or an absolute increase of 0.5 mg/
CTA indicates computed tomographic angiography; and N/A, not available.
*Measured using a RadCal AccuProbe meter equipped with a 20×5-3 ion chamber and a human head phantom. The above radiation doses conform to the 2012 International Commission on Radiological Protection guidelines.

**Table 2. Mean Effective Radiation Dose With Our Protocol for Multimodal Imaging, Including Multiphase CTA When Compared With a Conventional Protocol for Multimodal Imaging**

<table>
<thead>
<tr>
<th>Type of Examination</th>
<th>Mean Estimated Effective Dose in an Established Center, mSv</th>
<th>Mean Estimated Effective Dose at Our Center, mSv</th>
<th>Radiation Dose to the Eye, mGy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unenhanced CT head</td>
<td>2.7±0.3</td>
<td>2.0±0.5</td>
<td>N/A</td>
</tr>
<tr>
<td>Routine CT angiogram head and neck</td>
<td>5.4±2.2</td>
<td>5.0±0.5</td>
<td>15</td>
</tr>
<tr>
<td>2 additional phases of multiphase CTA</td>
<td>N/A</td>
<td>1±0.5</td>
<td>45</td>
</tr>
<tr>
<td>Smart preparation</td>
<td>0.1±0.1</td>
<td>0.1±0.1</td>
<td>N/A</td>
</tr>
<tr>
<td>Total dose</td>
<td>8.2</td>
<td>8.1</td>
<td></td>
</tr>
<tr>
<td>CT perfusion</td>
<td>4.9±0.0</td>
<td>3.5±0.5</td>
<td>200</td>
</tr>
<tr>
<td>Postcontrast CT head</td>
<td>2.6±0.2</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

CCT is the gold standard when evaluating TCD for occlusion detection. TCD is only able to detect skull base/proximal occlusions and has limited accuracy when compared with CTA as the gold standard but can be complementary to CTA in the acute setting given the dynamic nature of stroke where changes in occlusion status can occur quickly.

With the advent of endovascular treatment, there has been increasing attention given to understanding recanalization rates with treatments, such as intravenous thrombolysis, to determine when endovascular treatment is necessary. This question on the need for additional endovascular treatment gains significant importance when patients arrive in primary stroke centers and have to be referred to endovascular capable tertiary hospitals. Important factors that influence systemic thrombolysis recanalization efficacy include thrombus extent and residual flow through the thrombus. Thrombus extent is measurable without requiring vascular imaging by the detection of the hyperdense artery sign most commonly seen in the M1 segment of the middle cerebral artery (MCA). Thrombus length was measured as length of arterial hyperdensities in admission nonenhanced CT images with a slice width of 1.25 to 2.5 mm. No recanalization was noted in any intravenous tPA patient with a thrombus length >8 mm. Thrombus detection on NCCT is not as reliable as CTA. In a series of horizontal segment MCA occlusions identified by CTA, only 43% had evidence of a hyperdense MCA sign on NCCT.

**Occlusion Detection and Thrombus Length**

Detection of the site of arterial occlusion has major implications for acute stroke management especially in the new era of endovascular treatment. All 3 modalities have been evaluated for occlusion detection. CTA has a higher sensitivity, positive predictive value, and inter-rater reliability compared with MRA for identification of an occlusion. CTA is considered the gold standard when evaluating TCD for occlusion detection. TCD is only able to detect skull base/proximal occlusions and has limited accuracy when compared with CTA as the gold standard but can be complementary to CTA in the acute setting given the dynamic nature of stroke where changes in occlusion status can occur quickly.

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**Intracerebral Hemorrhage**

A growing body of evidence suggests that there may be considerable utility in performing noninvasive vascular imaging during the acute to early phase of intracerebral hemorrhage (ICH). Because NCCT remains the parenchymal imaging tool of choice in acute stroke to rule out ICH in all patients presenting with acute disabling stroke symptoms, CTA can be performed immediately after NCCT while still on the CT table and not be delayed awaiting blood testing for creatinine level. The one circumstance where caution is still needed is in nonhemodialysis patients with known severe renal insufficiency (estimated glomerular filtration rate, <25), where CTA should be avoided in most instances.

CTA indicates computed tomographic angiography; and N/A, not available.
*Measured using a RadCal AccuProbe meter equipped with a 20×5-3 ion chamber and a human head phantom. The above radiation doses conform to the 2012 International Commission on Radiological Protection guidelines.
also has the added advantage of being able to evaluate not only occlusion site but also thrombus burden/length and residual flow together. These imaging parameters on CTA can help physicians estimate the likelihood of early recanalization with tPA. Patients with residual flow within the clot were 5× more likely to reperfuse than those without it. Patients with residual flow and a shorter clot length (≤15 mm) were most likely to reperfuse (70.6%). Patients with proximal M1 clots without residual flow reperfused only 8% of the time and carotid-T/L occlusions rarely reperfused (1.7%).41

**Leptomeningeal Filling/Collateral Assessment**

There is a large body of evidence to suggest that leptomeningeal collaterals play an important role in maintaining blood flow to brain regions distal to an arterial occlusion.42 Imaging assessment of leptomeningeal collaterals in humans does not
visualize these vessels directly but instead relies on an indirect assessment of the extent and rate of backfilling of pial arteries receiving blood flow through these small interarterial connections.43–46 Angiographic grade of collateral flow strongly influences the rate of hemorrhagic transformation after therapeutic recanalization for acute ischemic stroke. Significant ICH risk (25.0%) has been seen in patients with poor pial collaterals especially when recanalization is achieved.47,48 There is a paucity of literature evaluating MRA and TCD to assess collaterals directly given the limitations of both techniques to evaluate the distal vasculature. Collaterals have been evaluated with MR perfusion source images, but this is not commercially available as yet.49 Many CTA-based collateral scoring systems have been published, which correlate collateral extent with clinical outcome. Good collateral status as assessed by CTA was significantly associated with small initial infarct volume, reduced infarct expansion, and more favorable functional outcomes.50–55 Patients with no collaterals had much larger infarcts on diffusion-weighted MRI than those with better collaterals.56 Patients with poor collaterals continue to have major infarct growth even in the presence of reperfusion.57 One challenge with the advent of fast spiral CT imaging is that image acquisition of brain is sometimes too fast on a single-phase CTA before collaterals have a chance to fill in. This misclassifies patients as having no collaterals when in fact collaterals are simply delayed. Such patients may still be good candidates for reperfusion treatment. CTA also has the added advantage of providing leptomeningeal backfilling information to estimate collaterals for both anterior cerebral artery–MCA and posterior cerebral artery–MCA collaterals, which is not possible with selective carotid injections performed with conventional angiography. Posterior cerebral artery–MCA collaterals are generally more robust with greater size, extent, and faster filling.58 In the Intervventional Management of Stroke (IMS-3) trial, baseline CTA collaterals were a robust determinant of final clinical outcome with maximal benefit with endovascular treatment seen in patients with intermediate collaterals.59 The Endovascular Treatment for Small Core and Anterior circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial was the first acute stroke trial to use CTA-based collateral assessment for selected patients. The ESCAPE trial excluded patients with poor or no collaterals.60 Noninvasive collateral assessment with CTA should now have a role in the endovascular treatment decision-making process.

### Catheter Access

Neurointerventional practice is now based on achieving recanalization using multiple devices and techniques tailored to the needs of a specific situation. All necessary information for procedural planning can be easily obtained by CTA and then reviewed by the interventionalist before initiating the procedure. Neurointerventionists require not only information on the site of occlusion but also the anatomy of the arch of aorta and proximal extracranial neck vessels. CTA provides high-resolution images of the arch of aorta and neck vessels that provide information on great vessel thrombi,61 aortic atherosclerosis,62 anatomic variants (ie, bovine or type 1–3 arch63), vessel angles, and tortuosity,64 which each can affect the planning and duration of the endovascular procedure.65,66 Access to the carotid circulation may require specialized access catheters to handle the curves and angles at bifurcation points. TCD/transcranial color Doppler and MRA are both impractical given the added time required to perform each test and the limited visualization of the great vessel anatomy each provides.

### Endovascular Treatment Trials Required CTA for Selection

The most compelling argument for vascular imaging, in particular CTA, is the recently completed endovascular treatment randomized trials in acute stroke. Each successful randomized controlled trial required the identification of a large vessel (M1 MCA or internal carotid artery) occlusion predominantly by CTA, and each consistently showed a robust clinical benefit of mechanical thrombectomy with predominantly stent retrieval devices compared with noninterventional approaches.67–71 Revisions to acute stroke guidelines are now published in several countries, which now confirm the level 1 evidence for endovascular treatment within a 6-hour onset to groin puncture time window.72–74 Noninvasive vascular imaging with modalities, such as CTA, are also mentioned in these guidelines to identify suitable candidates for endovascular treatment by the detection of a proximal intracranial occlusion.75
Emerging Vascular Imaging Technologies
Many recent technological advances are revolutionizing how we can evaluate the cerebral vasculature. Methods to provide temporal resolution during the CTA acquisition allows for capture of critical information over time. The current standard of single-phase CTA is a snapshot in time that can miss crucial pathophysiology, such as slow flow versus thrombus, delayed collateral backfilling, or delayed contrast leakage (ICH) that is best appreciated with imaging several seconds after peak arterial phase acquisition. Dynamic CTA or 4D CTA is a technique that derives time-resolved images of pial arterial filling from perfusion CT images. It requires postprocessing and whole-brain perfusion CT. Multiphase CTA is an alternative technique that generates time-resolved cerebral angiograms of brain vasculature from the skull base to the vertex in 3 phases after contrast injection. It identifies crucial pathophysiology, such as slow flow, delayed collateral filling, and delayed contrast leakage (ICH), similar to 4D CTA. Aortic arch to vertex CTA is performed with a multidetector CT scanner during the first phase of acquisition timed to capture the peak arterial phase in a healthy brain for 7 s. The remaining 2 phases are from the skull base to the vertex in the equilibrium/peak venous and late venous phases by the movement of the CT gantry over the cranium ≈8 s apart. Multiphase CTA has advantages, including the speed of acquisition and interpretation, minimal additional radiation, no additional contrast material, whole-brain coverage, and no postprocessing. Advances in vascular MRI include improvements in visualization of vessel wall abnormalities, which may have a role in acute stroke investigation. Microparticles of iron oxide can detect inflammatory molecules (molecular MRI), bright blood and black blood high-resolution MRI can evaluate vulnerable carotid and intracranial plaque, and thin-section multicontrast vessel wall MRI can examine different intracranial vascular pathologies. Compressed sensing allows for dynamic (time resolved) contrast–enhanced MRA imaging that could include collateral filling. Ultrafast Doppler imaging is a novel technique to quantify blood flow and anatomically mapping of blood vessels, but it is still in the developmental stage. Advances in transcranial color sonography include vascular enhancement technology and 3D-TCCS, which increase clarity and reliability of vessel imaging.

Suggested Time-Efficient but Clinically Comprehensive NCCT/Multiphase CTA Protocol
In Tables 3 and 4, we provide a suggested workflow process and protocol for an acute stroke NCCT and multiphase CTA for both ischemic stroke and ICH. This workflow encourages a time-efficient use of CTA with careful interpretation of NCCT and CTA-specific imaging process methods at each step. This protocol limits radiation exposure and contrast dose and is rapidly obtained (3–5 minute total time on the CT table) to provide the stroke clinician and radiologist all the necessary clinically relevant components of the vasculature, such as occlusion site(s), thrombus extent, and collateral backfilling, for efficient treatment decision making and procedural planning.

Conclusions
The time has come for the standard inclusion of vascular imaging in all initial acute stroke assessments. CTA has many advantages compared with other modalities and should become the standard for assessment of patients with acute disabling stroke worldwide. The recent endovascular trials all required the detection of a proximal large-artery occlusion by CTA. To minimize delay, it should be done immediately after the NCCT while the patient is still on the CT table without information about kidney function. Time-resolved CTA in the form of dynamic CTA or multiphase CTA is poised to provide additional information on delayed collateral backfilling and thrombus extent, which further influences acute stroke decision making. Future phase 2 clinical trials of reperfusion treatment could also benefit from proof-of-concept surrogate outcome assessment of recanalization by baseline and follow-up CTA before large phase 3 trials are initiated.

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Dr Demchuk received honoraria for speaking at Continuing Medical Education events for Covidien/Medtronic. Dr Menon has a patent pending for systems of triage in acute ischemic stroke. Dr Goyal has a consulting agreement with Covidien/Medtronic for design and conduct of SWIFT PRIME trial and for teaching engagements. Dr Goyal has a licensing agreement with GE Healthcare for systems to improve stroke diagnosis (patent pending). As principal investigators of the Endovascular Treatment for Small Core and Anterior circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial, Drs Goyal and Demchuk received an unrestricted research grant to the University of Calgary from Covidien to support funding for ESCAPE trial.

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