



Advanced ED Stroke Patient Diagnostics: Can the Use of Advanced Diagnostics (CTP/CTA, MRI/MRA) Be Utilized to Improve Patient Care?

Andrew Asimos, MD, FACEP

Director of Emergency Stroke Care
Carolinas Medical Center
Charlotte, NC

Adjunct Associate Professor
Department of Emergency Medicine
University of North Carolina School of Medicine
Chapel Hill, NC

Case Presentation

A 49 year old Vietnamese male is found by his wife at 6:30 am unable to speak. He had spilled his coffee and seemed clumsy. It was not clear if he had symptoms upon awakening, but he had walked downstairs after awakening. He is brought to the ED around 9:45 am by his family. On initial exam, he is mute, not attempting speech. He does follow a few verbal commands, but is inconsistent with commands. He has some mild right facial movement, only trace movement in the right arm, and 4/5 right leg weakness. His heart rate is regular. Blood pressure is 140/70. The patient is a smoker and does not drink alcohol. He is on no medications. A non-contrast head CT demonstrates “no acute lesion”. Three dimensional reconstructions of the CTA demonstrate a proximal left MCA occlusion. His CTP shows a blood flow/blood volume mismatch in the left MCA distribution.

Key Clinical Questions and Learning Points

What is the purpose of the initial neuroimaging in the diagnosis of ED stroke patients?

The goal of initial neuroimaging for presumed acute stroke patients is assessing the so-called “Four P’s”: Parenchyma, Pipes, Perfusion, and Penumbra. *Parenchymal* evaluation will detect early signs of acute stroke and rule out hemorrhage. Evaluation of the *pipes* assesses intracranial and extracranial circulation for evidence of intravascular thrombus. Indices of *perfusion* include cerebral blood flow, blood volume, and mean transit time measurements, which will ultimately yield assessment of penumbra. *Penumbra* refers to tissue at risk of dying if ischemia continues. A secondary goal of acute neuroimaging in stroke is to provide information that enhances the risk/benefit analysis in considering acute therapeutic interventions.

What is the role of MRI in the initial evaluation of ED stroke patients?

Multimodal MRI/MRA, including DWI interpreted with concurrent perfusion techniques, fulfills the goals stated above. If availability and cost were not an issue, based on the currently available data, multimodal MRI/MRA would be the preferred imaging modality for acute stroke. It allows for whole brain coverage of the penumbra/infarct ratio, can detect lesions such as microbleeds (that may increase the risk of hemorrhage after treatment with thrombolytics), and does not require radiation. On the other hand, CT is less time consuming than MRI, monitoring of patients in CT is easier, CT generally is less costly than MRI, and CT is more widely available in emergency department settings.

How can CTP/CTA or MRI/MRA be utilized in order to optimize the use of IV tPA and the triage of ED stroke patients for advanced IR therapeutics?

Assessment of the Four P's supplants the need to rely on a somewhat arbitrary absolute time window for treatment. Evaluation of the penumbra/infarct ratio, which is enabled by these advanced imaging techniques, will determine if there is salvageable brain. By assessing clot burden and the extent of salvageable penumbra, the potential benefit of advanced IR techniques can be considered.

How can CTA (MRA) be utilized to detect the site of the vascular occlusion, and CTP (DWI/PWI) the size of the ischemic penumbra and the infarct core?

CTA and MRA provide easily interpretable images reflecting vessel patency and clot burden, especially with 3-dimensional, post-processing reformatting. For penumbral delineation, recent studies have increasingly validated CTP in this application. Mismatches on CTP (between cerebral blood flow and cerebral blood volume) and MRI (between DWI and PWI) distinguish salvageable penumbra from irreversibly injured infarct. Trials such as the DIAS and DEDAS have successfully incorporated these modalities for penumbral assessment selection.

How can CTP/CTA (MRA/MRI) be utilized to maximize the potential benefit and minimize risk when using IV tPA in ED stroke patients?

Most importantly, advanced neuroimaging techniques definitively diagnose an acute ischemic stroke. CTP pioneers such as Wintermark have demonstrated that CTP is more accurate than unenhanced CT for detecting stroke and determining the extent of stroke. By distinguishing penumbra from infarcted tissue, potential benefit of tPA can be assessed. More recent data, such as that provided by the DEFUSE study, have derived baseline MRI profiles that identify patient subgroups likely to benefit from reperfusion therapies and potentially identify subgroups unlikely to benefit or who may be harmed. This evolving data indicates that there is a malignant MRI profile for patients who do badly and who are at particularly high risk of ICH following reperfusion. Alternatively, these data reveal a target mismatch profile population who have a favorable clinical outcome if treated with thrombolytics.

What are perfusion scans, what do they demonstrate, and how are they interpreted in the ED?

CTP scanning includes measurements of cerebral blood flow (CBF), cerebral blood volume (CBV), and Mean Transit Time (MTT). Perfusion refers to the steady-state delivery of blood to cerebral tissue through the capillaries. CBF is the volume flow rate of blood through the cerebral vasculature per unit time. CBV is the amount of blood in a given amount of tissue at any time. MTT is the average time it takes for blood to traverse from the arterial to the venous side of the cerebral vasculature. CTP imaging in acute stroke is based on the hypothesis that the *penumbra* shows either increased MTT, with moderately decreased CBF and normal or increased CBV secondary to autoregulatory mechanisms, or increased MTT with markedly reduced CBF and moderately reduced CBV. Alternatively, infarcted tissue shows severely decreased CBF and CBV, with increased MTT. Based on Wintermark's latest work, an absolute CBV threshold at 2.0 ml/100 g provides the most accurate delineation of the acute infarct core, while a relative MTT threshold at 145% affords the most accurate delineation of the tissue at risk of infarction in the absence of recanalization.

What softwares or technologies are necessary in order to allow these tests to be used quickly and real time when deciding the use of IV tPA and other stroke therapeutics?

CTA typically involves a volumetric helical acquisition that extends from the neck to the intracranial vasculature. The examination is performed using a time-optimized bolus of contrast material for vessel enhancement. Postprocessing is performed at a 3-dimensional display workstation to generate multiplanar reformatted images and maximum intensity projection images. CT perfusion imaging can be performed quickly on any standard helical CT scanner immediately after unenhanced CT. CT perfusion maps can be generated quickly at a workstation in the CT scanning area. The one limitation of CTP imaging is that it does not allow for whole brain coverage. The evaluation of perfusion imaging data requires the use of complex deconvolution algorithms to produce perfusion maps. The two most commonly used CT perfusion imaging techniques are dynamic contrast material-enhanced perfusion imaging and perfused-blood-volume mapping. Software is available from different vendors that generate CTA and CTP images, but quality of the final images obtained can be highly dependent on the parameters set by and overall performance of the CT technician.

What can be done by interested emergency physicians in order to develop these capabilities in their own Emergency Departments?

EM practitioners interested in incorporating these techniques into their acute stroke evaluation protocols must work closely with their institutional neuroradiology, neurology, and endovascular therapy colleagues. Importantly, since performance of these studies is highly CT technician dependent, those individuals must be involved in the process. Protocols developed based on the most recent data can be developed, but will need to be re-evaluated regularly, due to the considerable ongoing and emerging research in this arena.

What usage of these advanced diagnostics are the standard of care in 2007, and why?

None of these advanced diagnostics is currently considered the standard of care. The most recently published guidelines (Adams HP et al. *Stroke* 2007;38:1655-1711.) and a recently published review on MRI diffusion perfusion mismatch (Kane I, Sandercock P and Wardlaw J. *Journal of Neurology, Neurosurgery & Psychiatry* 2007;78:485-91.) do not yet endorse the use of advanced diagnostics in treatment decisions. The guidelines published in *Stroke* only state that “Multimodal CT and MRI may provide additional information that will improve diagnosis of ischemic stroke . . . Emergency treatment of stroke should not be delayed in order to obtain multimodal imaging studies . . . Vascular imaging should not delay treatment of patients whose symptoms started <3 hours ago and who have acute ischemic stroke”. The recently published systematic review of MRI concluded that “standardized definitions of mismatch and perfusion are needed and that more data are needed from studies including patients with and without mismatch, and randomized treatment allocation, to determine the role of mismatch.” Unfortunately, published guidelines and reviews cannot keep up with the emerging literature in this area. For example, a quick search on MEDLINE® reveals that about 50 papers on CT Perfusion imaging alone in stroke have been published since the studies referenced in the latest guideline, and the MRI review only considered work published before May of 2005.

Imaging of Acute Stroke

Muir KW et al. *Lancet Neurology* 2006;5:755-768.

State of the Art Imaging of Acute Stroke

Srinivasan A et al. *Radiographics* 2006;26:S75-S95.

Both of these reviews describe how the pathophysiology of the ischemic penumbra can now be assessed with CT or MRI-based perfusion imaging techniques. They explain how information from these advanced imaging studies can allow targeted therapy in individual patients and potentially extend the time window for reperfusion therapy.

Accuracy of dynamic perfusion CT with deconvolution in detecting acute hemispheric stroke

Wintermark M et al. *Am J Neuroradiol* 2005;26(1):104-12.

This work helped confirm that dynamic CTP maps are more accurate than nonenhanced CT in detecting hemispheric strokes and that CTP is highly reliable for assessing the extent of stroke.

Perfusion-CT assessment of infarct core and penumbra: receiver operating characteristic curve analysis in 130 patients suspected of acute hemispheric stroke

Wintermark M et al. *Stroke* 2006;37:979-985.

In a series of 130 patients, this study concluded that the optimal approach to define the infarct and the penumbra is a combined approach using 2 CTP parameters: relative MTT and absolute CBV, with dedicated thresholds. The CTP parameter that most accurately describes the tissue at risk of infarction in case of persistent arterial occlusion is the relative MTT, with an optimal threshold of 145%. The CTP parameter that most accurately describes the infarct core on admission is the absolute CBV, with an optimal threshold at 2.0 ml×100 g-1.

Comparison of CT perfusion and angiography and MRI in selecting stroke patients for acute treatment

Wintermark M et al. *Neurology* 2007;68(9):694-697.

This paper compared perfusion CT P/CTA and MRI examinations in 42 patients within 3 to 9 hours following symptom onset. Fourteen patients would have been suitable candidates for reperfusion treatment based on MRI findings. Correlation between CTP/CTA and MRI was excellent for infarct size, cortical involvement, and internal cerebral artery occlusion and substantial for penumbra/infarct ratio. It concludes that relying on MRI or CTP/CTA would have led to the same treatment decisions in all cases but one.

Identification of the penumbra and infarct core on hyperacute noncontrast and perfusion CT

Parsons MW et al. *Neurology* 2007;68(10):730-6.

This recent paper provides increasing validation of penumbral delineation via CTP versus noncontrast CT.

Magnetic resonance imaging profiles predict clinical response to early reperfusion: the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study

Albers GW et al. *Annals of Neurology* 2006;60(5):508-17.

This study's goal was to determine whether prespecified baseline MRI profiles could identify stroke patients who have a robust clinical response after early reperfusion when treated with IV tPA 3 to 6 hours after symptom onset. Early reperfusion was associated with significantly increased odds of achieving a favorable clinical response in patients with a perfusion/diffusion mismatch (OR 5.4; $p = 0.039$) and an even more favorable response in patients with the Target Mismatch profile (OR 8.7; $p = 0.011$), while patients with the No Mismatch profile did not appear to benefit from early reperfusion. Importantly, early reperfusion was associated with fatal intracranial hemorrhage in patients with the Malignant profile. They concluded that for stroke patients treated 3 to 6 hours after onset, baseline MRI findings can identify subgroups likely to benefit from reperfusion therapies and can possibly identify those not likely to benefit or who may be harmed.

Guidelines for the Early Management of Adults with Ischemic Stroke

Adams HP et al. *Stroke* 2007;38:1655-1711

These guidelines include recommendations for neuroimaging of acute stroke, but suffer from the limitation of excluding evaluation of much of the recent work that has been done in these arena.

Magnetic resonance perfusion diffusion mismatch and thrombolysis in acute ischaemic stroke: a systematic review of the evidence to date

Kane I, Sandercock P and Wardlaw J. *Journal of Neurology, Neurosurgery & Psychiatry* 2007;78(5):485-91.

This recently published review concluded that “currently data available on mismatch” are too limited to guide thrombolysis in routine practice. However, it only included studies published through May of 2005. It concluded that standardized definitions of mismatch and perfusion are needed and that more data are needed from studies including patients with and without mismatch, and randomized treatment allocation, to determine the role of mismatch.

Patient Case Outcome

From the introductory clinical case, the following is an example of how the ED medical record can be documented as the patient is examined, treated, and dispositioned.

ED History & Physical Document

- 49 year old Vietnamese male
- Found by his wife about 3 ½ hours prior to ED arrival unable to speak
- Unclear if awoke with symptoms, but did climb down stairs after awakening
- Brought to the ED by his family and evaluated immediately upon arrival
- Smoker, no alcohol use
- No known medications

- Vital signs: BP 140/70, pulse ox 98% on room air, POC glucose 133
- HEENT: Pupils midrange, reactive, no papilledema, airway OK
No head trauma noted
- Neck: No Bruits
- Chest: BSBE No Rales
- Cardiac: Regular rate and rhythm, no gallops or murmurs
- Abd: Soft, non tender, no organomegaly
- Ext: No pedal edema evident
- Skin: No rash, warm and dry
- Neuro: Awake, alert, with preferential right sided gaze
- CN: PEERL, left preferential gaze, droop of right lower face, palate moves symmetrically, right shoulder shrug weak, tongue midline

- Motor: 1/5 strength RUE and 4/5 RLE, 5/5 LUE and LLE
- Sensory: Decreased pinprick on right face, arm, and leg
- Reflex: 3+ right bicep, knee, and ankle, toe upgoing on the right; 2+ left bicep, knee, and ankle, toe downgoing on the left

- Cerebellar: Heel to shin with WNL bilaterally
- Language: profound expressive and receptive aphasia
- LOC: awake
- NIHSS: 17

Initial ED Management

- Non-contrast head CT scanning demonstrated no acute lesion
- Three dimensional reconstructions of the CTA demonstrated absence of left MCA flow
- CTP showed a blood flow/blood volume mismatch in the distribution of the left MCA.
- CBC and metabolic tests normal
- PT normal
- EKG - NSR
- **Diagnosis:** Acute left MCA distribution ischemic stroke

Hospital Course and Patient Outcome

After the perceived risks and benefits of an endovascular procedure were discussed with the patient and his family, he was taken to the angiography suite. Clot in the left ICA, as well as the right MCA were identified. The left ICA was opened with balloon angioplasty, and a carotid stent was placed. A portion of the MCA was opened with the combination of the Merci retriever device, intra-arterial t-PA, and balloon angioplasty.

At six month follow-up, his speech was clear, although he had some hesitation with speech. He had 5-/5 strength on the right side. NIH stroke scale score was 1.