Advanced Neuroimaging for Acute Stroke and Subarachnoid Hemorrhage: What is the Role of CTA, CTP, and MR Techniques?

CT angiography (CTA), CT perfusion (CTP), and MR scanning are increasingly available for the evaluation of acute stroke patients. Are CTA, CTP, and MR more accurate than non-contrast CT for detecting stroke and determining its extent? What data supports the ability of these modalities to distinguish the irreversibly infarcted brain from brain tissue that may be salvageable with reperfusion therapy? Can CTA or CTP parameters help predict the likelihood of hemorrhagic transformation of an ischemic stroke or growth of a hemorrhagic stroke? The speaker will address these questions and more.

- Provide an overview of the acquisition and derivation of CTA, CTP and MR images and the concept of the ischemic penumbra.
- Incorporate the concept of the ischemic penumbra into practice to improve quality of care to stroke patients.
- Discuss CTP and MR parameters that suggest infarction or hemorrhage.
- Discuss CTP and MR parameters that suggest ischemic penumbra to increase the efficiency of communications with radiology and neurology consultants.

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Case #1

A 54 year old male is found by his wife at 6:30 am unable to speak. It was not clear if he had symptoms upon awakening, but he was “normal” when he went to bed at 10:30 pm last night. He is brought to the ED around 9:45 am by his family. On initial exam, he is aphasic. He does follow a few verbal commands, but is inconsistent. He has right facial droop, only trace movement in the right arm, and 4/5 right leg weakness. His heart rate is regular. Blood pressure is 175/90. The patient is a smoker and does not have a history of hypertension. He is on no medications. A non-contrast head CT demonstrates “no acute lesion”.

Advanced Neurological Imaging

The goal of initial neuroimaging for patients presenting with an acute neurological deficit 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, dissection or leak. 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 a lack of perfusion continues. Normal brain blood flow is 40cc/100g brain tissue. When blood flow is less than 20-25cc/100g of brain tissue the neurons shut off. This makes up the area of the penumbra where collateral circulation maintains enough oxygenation to prevent membrane break down. When blood flow is less than 10cc/100g of brain tissue membrane break down occurs. This is the infarct core.

MR Perfusion, MR Diffusion and MR Angiography

Magnetic Resonance Imaging (MRI) historically has two drawbacks for its use in the diagnosis of acute neurological deficits. First, is the time required to complete the study, often 30 to 60 minutes. The second is overall availability and cost. Multimodal MRI consists of several new technologies. Diffusion-weighted imaging (DWI) allows for identification of the core infarct by detecting extracellular water collection. Perfusion-weighted imaging (PWI) detects areas of hypoperfusion of gadolinium thus finding both the core and penumbral areas. Digital subtraction, or DWI/PWI mismatch, therefore allows for determination of the penumbral area alone and hence the area to be targeted for reperfusion. If there is no mismatch, then no penumbra exists worth attempting recanalization. When comparing CT with MRI there has been found to be good correlation of early ischemic changes on CT scan with larger lesion on DWI looking at the middle cerebral artery distribution. Gradient Recalled Echo (GRE) pulse sequence MR allows for detection of an area of increase signal intensity that corresponds to recently extravasated blood by detecting levels of oxyhemoglobin. Areas of low signal intensity correlate with areas of deoxyhemoglobin or methemoglobin. This may allow for detection of hyperacute cerebral hemorrhages. MR angiography (MRA) provides detailed mapping of the cerebral arteries allowing for pin point assessment of the occluded or leaking artery. This allows diagnoses to be made in vague cases and allows treatment strategies to be formulated.
CT Perfusion (CTP) and CT Angiography (CTA)

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. 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%, and where normal is 100%, affords the most accurate delineation of the tissue at risk of infarction in the absence of recanalization.

Changes in Cerebral Vascular Physiology with Worsening Circulatory Impairment

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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. Post processing is performed at a 3-dimensional display workstation to generate multiplanar reformatted images and maximum intensity projection images. Software is available from different vendors that generate CTA, but quality of the final images obtained can be highly dependent on the parameters set by and overall performance of the CT technician.

CT Perfusion

Advantages:
- Produces fewer motion artifacts than with MR imaging.
- Can be completed in 5 to 10 minutes.
- Provides good visualization of major structures.
- Uniformly available.
- Provides information on salvageable penumbra.
- Has overall accuracy of 90% to 100%
- Can be used in patients with pacemakers, defibrillator, or claustrophobia

Disadvantages:
- Exposes patient to ionizing radiation.
- Low resolution for small parenchymal abnormalities.
- Risk of contrast reactions.
MR Diffusion/Perfusion Imaging

**Advantages:**
- Well defines brain parenchyma.
- Provides early detection of ischemic changes.
- Does not expose patient to ionizing radiation.
- More effective than CT for identifying small ischemic strokes.

**Disadvantages:**
- Limited availability compared with CT and after hours.
- Patient contraindications such as claustrophobia, metal implants, and pacemakers.
- Examination is lengthy (up to 60 minutes).
- Risk of gadolinium reaction.

**Using CTP/CTA and MRI/MRA**

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. Patients are enrolled from 3-6 hours only if there is at least a 20% penumbra. We may be switching from “Time is brain to physiology is brain”. 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 has a favorable clinical outcome if treated with thrombolytics.

CTP is not without controversy. In 2009 the FDA issued a warning about the use of CTP in stroke patients based on a concern for radiation exposure at one site in California. Millisievert (mSv) is one unit of measure for radiation. We experience roughly 2 mSv per year from background radiation. One chest xray is 0.1 mSv and a normal CTP is 4 mSv. The patients of concern were receiving 8 times the normal amount, or approximately 32 mSv. They experienced hair loss. It was determined that the CT scanner was set at the wrong radiation intensity. This prompted increased safety checks prior to any scan to assure that the minimum allowable dose of radiation is being used.

In Europe CTP is being used to extend the window for thrombolysis treatment beyond 4.5 hours. Criteria include must have less than 1/3 middle cerebral artery infarct and have at least 20% penumbra. In Spain they are finding that good long term outcome was 64% and 60% when
comparing <4.5 hours vs. >4.5 hours (average time from onset 508 minutes), and symptomatic hemorrhage rates were similar, 2.9% vs. 2.3%.

CTP is also being evaluated to determine if there are a group of patients that should not be treated with thrombolysis even if they are within the 3 hour window. The malignant profile is based on a Tmax of >8 seconds and blood volume > 85 ml. This is seen in 10% of patients. In one small study this had a 100% sensitivity for predicting a bad outcome (modified Rankin of 5 or 6) with a 40% symptomatic hemorrhage rate.

One potential use for CTP is patients in whom the onset time is unknown particularly in “wake up” strokes. In these patients CTP can determine if penumbra exists and therefore treatment is warranted. One small study revealed that this type of protocol is feasible but others need to be done because there were protocol violations and CTP reading inconsistencies. Some are concerned over the possibility of false penumbras. This can happen with physiologic oligemia or even with head position in the scanner.

None of these advanced diagnostics is currently considered the standard of care. The most recently published guidelines 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”. Unfortunately the data used to formulate the current guideline (published in 2007) is now 3-5 years old and there are many more studies delineating the usefulness of these new imaging modalities.

**Case Conclusion**
- 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

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 left 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 in the right arm.

**Key Learning Points**
1) CTP/CTA provides information about the 4 Ps, parenchyma, pipes, perfusion and penumbra.
2) MRI/MRA provides equally good detail but may not be available or is difficult to utilize. Vague or transient symptoms may reveal lesions on MRI.
3) CTP/CTA allow differential diagnoses to be narrowed
4) As CTP use progresses “time is brain” may be replaced by “physiology is brain”
Reference List


Inoue M, et al. *Stroke* 2012;43:00-00.

Johnson M, *Radiologic Technology* 2012;83:467-486.


