MR and CT Perfusion in Acute Ischemic Stroke

The uses, methods, and risks associated with these alternative imaging modalities.

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Treatment of acute ischemic stroke is based on the fundamental concept of differentiating infarction core from the surrounding ischemic penumbra. The infarction core represents an area of brain tissue that has suffered irreversible ischemic damage and cellular death. The ischemic core is not salvageable even after reperfusion. In fact, revascularization of the ischemic core can result in hemorrhage. The major target of intervention in acute ischemic stroke treatment is the ischemic penumbra. This region of brain tissue surrounding the ischemic core is salvageable and has reversible ischemia. The ischemic penumbra is hypoperfused, but blood flow is adequate to prevent cellular membrane breakdown and mitochondrial death. However, the blood flow reduction in the ischemic penumbra can be severe enough to cause neuronal electrical failure. Ongoing ischemia may result in metabolic derangements and cellular death, unless collateral formation or large-vessel reperfusion is achieved in a timely fashion.[1] Imaging of brain perfusion in acute stroke enables quantification and location of the ischemic penumbra and helps differentiate between salvageable brain tissue, which requires urgent revascularization, and dead brain tissue. Brain tissue that is beyond salvage can be identified. Reperfusion of dead brain tissue usually results in reperfusion hemorrhage. Consequently, applying brain perfusion techniques in patients with acute stroke can pinpoint the patients that will benefit most from revascularization and prevent the use of revascularization techniques in patients with dead brain tissue.

The most accurate definition of ischemic penumbra in human stroke derives from positron emission tomography studies that allow quantitative cerebral blood flow (CBF) and brain tissue metabolism determination.[2]

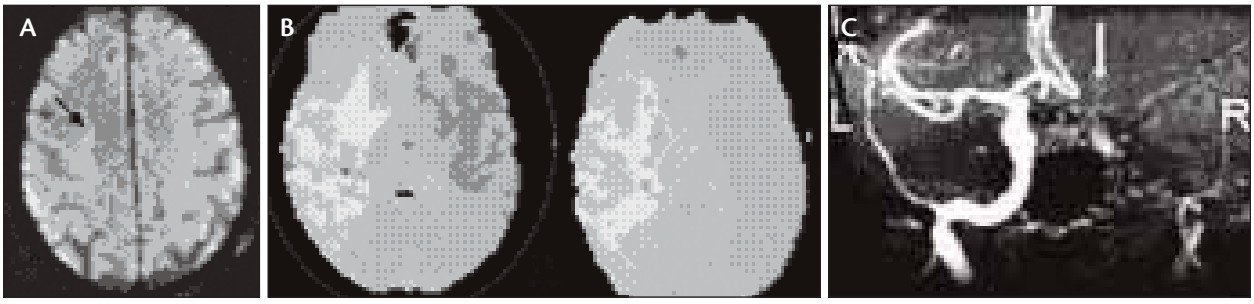

Figure 1. Magnetic resonance imaging (MRI). MR diffusion showing a small area stroke (arrow) (A). MR perfusion showing a large right hemispheric perfusion defect (B). MR angiogram with occlusion of right internal carotid artery and no-filling right middle cerebral artery; both anterior cerebral arteries fill from the left internal carotid artery (C).

However, positron emission tomography studies are expensive, require extensive technical support, and are time consuming,[2] making them impractical in hyperacute stroke settings with a time-limited opportunity of intervention. Alternative imaging modalities that are able to assess brain perfusion, tissue viability, and brain tissue at risk will be presented in this article, with specific emphasis on the role of MR and computed tomography (CT) perfusion in acute ischemic stroke management.

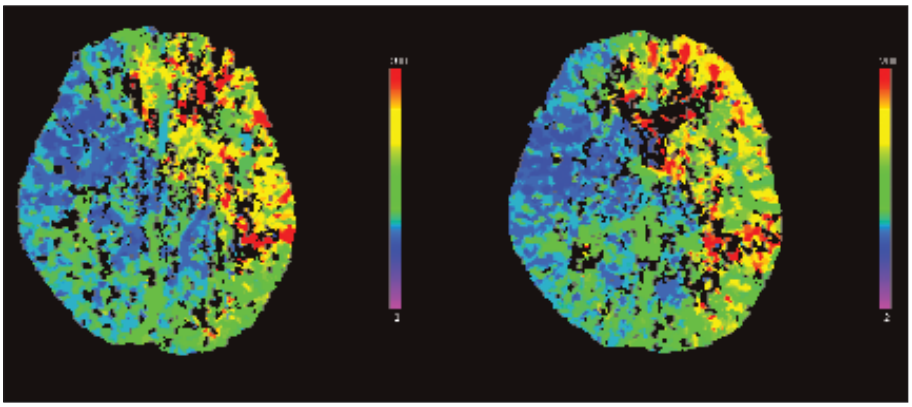

Figure 2. CTP image slice at the level of the frontal horn of the lateral ventricle and the third ventricle. Ischemic penumbra can be seen in the distribution of the left middle cerebral artery. The color map depicts red as poor flow and blue-green as normal flow. These images display ischemic penumbra without ischemic core (Somatom Sensation 64-slice CT scanner, Siemens Healthcare, Malvern, PA).

DIFFUSION AND PERFUSION MR IMAGING

During the last 2 decades, MRI techniques have gained an increasing role in acute stroke management. Animal and human studies have demonstrated that diffusion-weighted imaging (DWI) combined with perfusion-weighted imaging (PWI) sequences including regional cerebral blood volume (rCBV), relative CBF (rCBF), and mean transit time (MTT) maps can accurately represent the ischemic penumbra and predict the final size of the infarct.[3] DWI is an advanced MRI technique that is able to detect water diffusion in brain tissue.[4] Compared to normal brain tissue, ischemic brain tissue water diffusion coefficients change and can be represented as signal intensity changes of MRI. DWI MRI correlates well with the cellular metabolism and cytotoxic edema and predicts an rCBF below 15 to 20 mL/100 g/min, allowing ultra-early diagnosis of stroke.[5] The protons on water molecules in ischemic areas have restricted diffusion and will generate hyperintense signals and display a correspondent signal drop on the apparent diffusion coefficient maps. Hyperintense lesions on DWI are considered the MR equivalent of the infarction core, whereas the mismatch between the DWI abnormal signal and perfusion deficit on PWI represents the ischemic penumbra (Figure 1). DWI and PWI enable the diagnosis of small-vessel stroke (lacunes). Patients with lacunar strokes can have severe deficits that mimic large-vessel occlusions but are caused by small-vessel occlusions. MRI techniques can help guide the use of intravenous thrombolytic and mechanical revascularization techniques.[6]

Initially considered a reflection of irreversible ischemic damage, DWI lesions are reversible to some degree. In cases of early reperfusion, these images can overestimate the ischemic penumbra. These hyperreperfused areas depict regions of benign oligemia rather than ischemia. Therefore, an ischemic lesion can be divided into four regions: ischemic core, reversible DWI lesions, penumbra, and benign oligemia; both penumbra and reversible DWI lesions are targets for early thrombolysis.[4]

Clinical Applications of DWI/PWI MRI

Patient selection for reperfusion therapy is facilitated by knowledge of the lesion's size and location, the size and relative ratio of the irreversible ischemic core and the salvageable tissue, and the age of the infarction. Ultimately, the size of the salvageable tissue plays the largest role.[7] DWI and PWI MRI studies allow one to determine the efficacy of thrombolytic therapy by comparing the pre- and postthrombolysis lesion volumes.[8] Several investigational studies have found a good correlation of DWI and PWI changes with the final infarct size measured by the follow-up T2-weighted imaging abnormality, with the clinical outcome expressed by the National Institutes of Health Stroke Scale and the Barthel Index.[9-11] PWI/DWI mismatch-based selection of candidates for reperfusion beyond 3 hours of the ischemic stroke onset has been tested in multiple clinical trials. The results of DIAS (Desmoteplase In Acute Ischemic Stroke),[12] DEDAS (Dose Escalation of Desmoteplase in Acute Ischemic Stroke),[13] and DIAS-2[14] have not demonstrated a definite clinical benefit of desmoteplase administration in patients with PWI/DWI mismatch between 3 to 9 hours of onset; however, individual cases have been mechanically recanalized based on DWI/PWI mismatch determination even beyond 8 hours after the stroke onset with variable clinical results.[15,16] The MR RESCUE

trial is underway to answer the question of whether MRI can be used to select patients for mechanical embolectomy with the Merci retriever (Concentric Medical, Mountain View, CA) up to 8 hours after onset.[17] The small series of cases that were MRI selected underwent combined intravenous/intra-arterial thrombolysis within 3 to 6 hours from onset with good clinical results.[18] The DEFUSE (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution) study[19] proved that early thrombolysis (between 3 to 6 hours of stroke onset) leads to a favorable clinical outcome in patients with DWI/PWI mismatch, whereas the early reperfusion was not beneficial in patients without mismatch. In EPITHET (EchoPlanar Imaging Thrombolysis Evaluation Trial),[20] stroke subjects with DWI/PWI mismatch between 3 to 6 hours of onset were randomized to receive recombinant tissue-plasminogen activator or placebo; recombinant tissue-plasminogen activator recipients displayed a lesser lesion growth than the placebo group.

Pitfalls of DWI/PWI Techniques

Other studies have found that acute DWI hyperintensities could not predict the lesion growth, DWI abnormality did not represent the irreversibly infarcted tissue, apparent diffusion coefficient values in the ischemic penumbra could not predict tissue at risk, DWI/PWI mismatch did not predict lesion growth, and the PWI abnormality overestimated the amount of tissue at risk. A more powerful predictive value of the volumetric evolution of the lesion has been attributed to the site of occlusion assessed by the MR angiogram findings.[21]

Even when fast-sequence MR techniques are used, data acquisition lags behind CT. In cases when patients are intubated and sedated, MR-compatible ventilators must be used. Motion artifact in agitated patients can produce images that are unusable, wasting precious minutes. Although DWI/PWI is more sensitive and specific than CT perfusion (CTP) patient management during MRI is more difficult and time consuming.

CTP METHODS

CTP images are obtained by injecting a 50-mL intravenous contrast bolus in a vein of the upper extremity. The time course of CT density measurements is monitored. As the intravenous contrast moves from the upper extremity to the brain, the density in the slices of brain

being monitored increases in regions without vessel obstruction. In regions with stenotic or occluded vessels, the time to maximum opacification (density) increases, and the runoff of contrast on the venous side slows. Rapid-fire CT sequencing allows the dynamic flow of contrast to be measured as time-to-peak (TTP) opacification, rCBV, and rCBF. The grayscale contrast in the images generated by the plain or dry CT scan (Figure 4) allows the physician to see a completed infarct and distinguish between the ischemic core and ischemic penumbra. This grayscale image is generated by differing x-ray absorption levels of different tissues and bone based on their densities. In CT perfusion imaging, the rate of intravenous contrast movement through the ischemic penumbra, infarct zone, and normal tissue are different. This enables color map images to be formed, differentiating these areas on the CT scan.

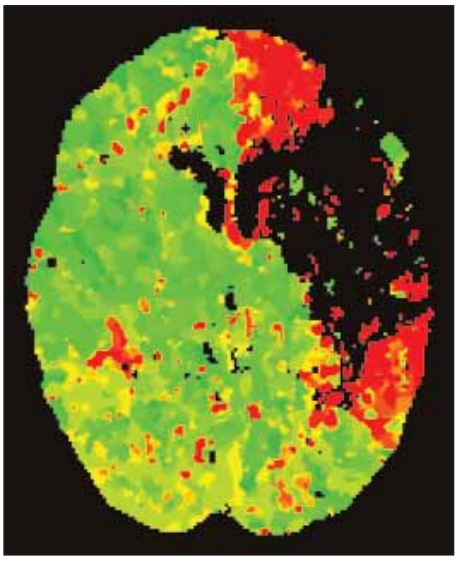

Figure 3. CTP image (Somatom Sensation 64-slice CT scanner) showing no flow in the distribution of the left middle cerebral artery. Notice the loss of signal in ischemic core surrounded by the ischemic penumbra. Because the salvageable tissue (ischemic penumbra) is smaller than the ischemic core, revascularization carries a high risk of hemorrhage.

Because of the difference in contrast absorption, ischemic core and ischemic penumbra have different linear attenuation coefficients—a quantity used in calculations to describe the penetration of materials by energy beams, which are x-rays in this case. If we divide a CT sample slice into volume elements, or voxels (the transmitted intensity [I_t] of an x-ray once it has passed through the sample of thickness), x voxels can be represented by the equation:

$$I_t = I_0 e^{-\mu x}$$

Incident radiation (I_0) is the initial radiation intensity of the x-ray, and μ is the characteristic attenuation coefficient of the sample. Assuming each voxel has its own attenuation coefficient (μ) based on its contrast absorption and subsequently density, the I_t of the first voxel will be used as the I_0 for the second voxel and so on for each successive iteration. It is only the final value of I_t, however, that can be measured by the scanner; none of the intermediate values for I_t are available. Therefore, it is only the sum of the individual voxel attenuation coefficients (simply Hounsfield units, unadjusted for standard temperature and pressure) that can be determined from the scan for a given sample of voxel width x. We cannot determine each voxel's individual attenuation coefficient; however, the sum is enough to generate the CT image with visible color differentiation between ischemic core and ischemic penumbra.

CTP in Acute Ischemic Stroke Management

CTP is an alternative imaging modality that is used in acute stroke settings and is designed to determine the severity and potential reversibility of neuronal damage and predict which brain tissue will be able to be salvaged with reperfusion (Figure 2) and which is irreversibly damaged (Figure 3).[23] CTP offers a number of practical advantages over other cerebral perfusion imaging methods: it can be performed immediately after unenhanced CT, it is fast (procedure time < 5 min), and it does not require specialized computer hardware.[23] There are two categories of CTP techniques that are currently used: whole-brain CTP and section-selective dynamic CTP. Whole-brain CTP provides information about the CBV and the infarct core with a reported sensitivity of 89.5% and 90.5%, respectively, without permitting assessment of the ischemic penumbra, which is the real target of intervention in acute ischemic stroke. Section-selective dynamic CTP is based on sequential CT data acquisition in a cine mode during an intravenous bolus of contrast agent, generating CBF, CBV, MTT, and TTP maps. When compared with noncontrast CT, MTT and TTP maps have better sensitivity in detecting acute hemispheric stroke (69.2% vs 77.6% and 76.5%, respectively), whereas CBF and CBV maps are significantly more specific (90.9% and 92.7%, respectively). False-negative results for dynamic CTP techniques are related to a lack of spatial coverage.[24] However, new CT technology from Toshiba America Medical Systems, Inc. (Tustin, CA) has enabled whole-brain perfusion imaging by increasing the size of the detector array.

Interaction terms such as *CBF X CBV* can differentiate between the infarction core and ischemic penumbra more reliably than CBF or CBV alone, with a sensitivity, specificity, and accuracy higher than 97%.[25] Infarction core is characterized by significant reduction of CBF

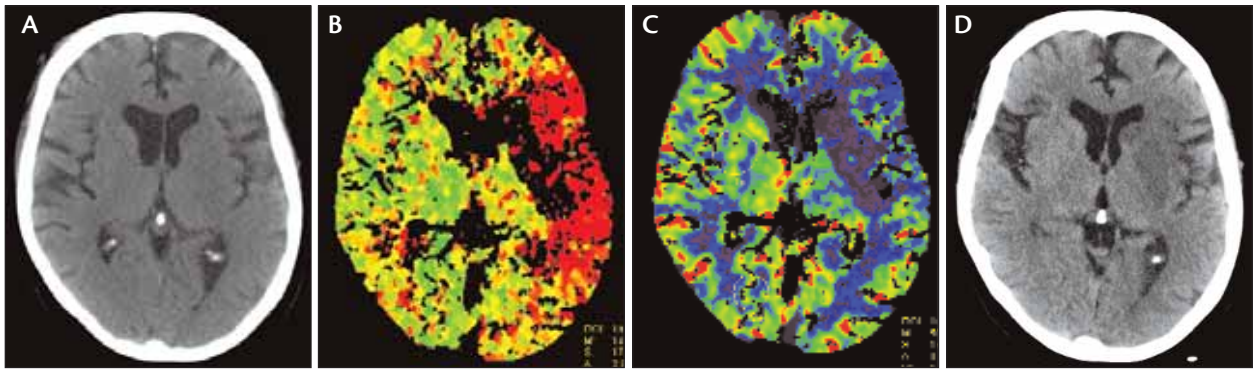

Figure 4. Case study: 77-year-old female patient with acute onset of dense right upper extremity paralysis and lower extremity weakness. Stuttering onset of symptoms 7 hours before presentation. CT without contrast axial slice at the level of the foramen of Monro, communication between the lateral and third ventricle (A). There is no evidence of intracranial hemorrhage or obvious infarction. TTP image shows the decrease in density in the left middle cerebral artery distribution (B). CTP image showing diminished CBV (C). The dark blue area indicates an ischemic core in the subcortical white matter of the left hemisphere. The previous CT without contrast did not display this ischemic core. CT without contrast the next day (D). The ischemic core predicted by CT perfusion images can now be seen in the caudate, putamen, and a portion of the subcortical white matter beneath the insula. This region was seen at the time of presentation in the CTP but not in the CT without contrast (Somatom Sensation 64-slice CT scanner).

accompanied by a matched decrease of CBV. In the infarct core, CBV falls despite a reduction of CBF. In salvageable tissue (ischemic penumbra), the CBV is maintained despite a reduction of CBF. The ischemic penumbra can be defined as an area of significant decrease of the CBF with no significant change of the CBV. Preservation of CBV indicates that this tissue demonstrates reversible ischemia. A threshold CBF/CBV value of 8.14 has been found to be > 94% sensitive and specific in differentiating between the infarction core and ischemic penumbra.[26] Threshold values that are able to differentiate infarct core from ischemic penumbra and normal tissue have been described for MTT (9.8 sec vs 5.2 sec vs 3.4 sec), rCBF (24.6 mL/100 g/min vs 64.8 mL/100 g/min vs 70.8 mL/100 g/min), and rCBV (3.5 mL/100 g vs 3.9 mL/100 g vs 2.9 mL/100 g), respectively.[27]

CTP source images of both arterial and venous phases may have the potential of being used as an assessment for infarct core and penumbra in acute ischemic stroke.[28]

Clinical Applications of CTP

The size of CTP abnormalities has been found to correlate with MR-DWI lesion size (r = 0.968) and MTT on the PWI map (r = 0.946);[29] also, a good correlation has been found between CTP-TTP-CBV and PWI-TTP-CBV.[30] Considering the larger accessibility, lower cost, and a performance equivalent to DWI/PWI techniques, CTP studies are routinely used in acute stroke management in large stroke centers.

Recently, CTP has proven to be a valuable tool for selecting acute ischemic stroke patients for systemic thrombolysis[31] or endovascular therapy[32] presenting outside of the accepted time window for treatment.[33] Recently, a good correlation between the stroke severity and CBV, CBF, and TTP abnormalities has been found, showing that CTP techniques are associated with a high sensitivity and positive predictive value of the short-term[34] or remote[35,36] clinical-functional outcome of stroke patients.

Pitfalls of CTP Techniques

Limited anatomical coverage by multislice detectors may compromise the diagnostic sensitivity of CTP, with special emphasis of reduced sensitivity for posterior circulation, small cortical, or lacunar strokes. Large doses of iodinated contrast may result in allergic reactions or contrast-induced nephropathy, particularly in diabetic patients. The radiation dose is moderately high, and the examination time may be prolonged in intolerant patients. However, the wider availability, fewer contraindications, easier patient monitoring, proven ability to exclude hemorrhage, and similar accuracy with MRI techniques may outweigh the limitations of CTP studies.[37]

CONCLUSION

MR and CT perfusion imaging has changed the methods we use to treat acute stroke patients. Prevention of reperfusion hemorrhage can be achieved in most cases by careful patient selection guided by

perfusion imaging. Although MR is more sensitive and specific in defining the size, location, and relationship between the ischemic core and the ischemic penumbra, this technique is time consuming and labor intensive. CTP is fast, easy, and accessible. As a result, CTP has become invaluable in the triage of acute stroke patients. Unfortunately, on most CT scanners, only a portion of the brain that is at risk can be interrogated using CTP techniques unless multiple 50-mL intravenous contrast boluses are used. Toshiba has recently produced the AquilionOne CT scanner with a large array of detectors capable of providing CTP of the whole brain with one 50-mL bolus of contrast. This will help prevent excess radiation and contrast administration to patients with acute stroke while providing information on the entire brain. ■

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