Recent Advances in MRI Technology in the Diagnosis and Treatment of Ischemic Stroke

Chung Y. Hsu, M.D. Ph.D.

Diffusion weighted imaging (DWI) has been widely used to study patients with acute ischemic stroke. While DWI is highly sensitive in depicting an ischemic lesion, its value in predicting final infarct volume during the acute stage has been called into question. However, when coupled with perfusion weighted imaging (PWI), a mismatch has been suggested to delineate reversible ischemic lesions that may be amenable to therapeutic interventions.

DWI and PWI

- When mismatched defects are present between DWI and PWI defined lesion, the mismatched tissues indicate regions of ischemic pneumbra.
- In contrast, when PWI/DWI defied lesion is matched, no salvageable tissues are expected.

A number of clinical trials of neuroprotective agents are ongoing in the US and other countries applying DWI/PWI in the selection of patients with salvageable brain tissue. However, the lack of quantitative measurements for the perfusion-weighted images and the definitions of the ischemic lesions are somewhat subjective, making it difficult to consistently determine the ischemic lesions.

Therapeutic window

- t-PA is the only FDA-approved therapy proven to be effective in patients with acute ischemic stroke.
- Population studies indicate that the therapeutic window for t-PA is only 3 hours after symptom onset.
- This imposes a major limitation on the clinical utility of t-PA treatment (only 1-2% of patients are treated)

Individualization of treatment?

- However, it is likely that the therapeutic window varies between individuals, depending on:
  - Variations in vasculature between individuals.
  - Collateral flow pattern.
  - Comobidities, temperature, etc.
- With the availability of acute therapies, there is an increasing need for methods to define the viability of ischemic brain tissue so that acute therapies can be more appropriately offered to patients and therapeutic windows can be individualized.

Compensatory Mechanisms

- CBF reserve.
- CBF autoregulation:
  CBF = CP/CVR CPP = SAP - ICP
- Supply-demand balance (affected by O_2, CO_2, pH, Hct, neuronal activity, diseases of the arteries and others.
- Oxygen Extraction Fraction (OEF): 30-90%

Brain Oxygen Metabolism (CMRO2)

- Normal CMRO2 can be maintained at 50-65% of normal CBF.
- Decompensation → Subnormal CMRO2.
  1. After maximal vasodilation
  2. After maximizing OEF
  3. Increase in metabolic demand (e.g., increased neuronal activity caused by Glutamate release, increased energy consumption secondary to IEG expression, DNA repair, seizures, etc.)

PET : Limitations

- Advantages
  - "Gold standard" for imaging pneumbra (CMRO2)
- Disadvantages
  - Requires multiple radiotracers with very short half-lives.
  - In-house cyclotron is needed to generate these tracers.
  - Long acquisition times (tracers must reach equilibrium).
  - Requires arterial line (problem for patients receiving thrombolysis).
  - Low resolution (voxel size - 1 cc).

MRI : Limitations

- Advantages
  - Noninvasive.
  - Does not involve radiation.
  - Relatively rapid image acquisition.
  - High resolution.
- Disadvantages
  - DWI lesion does not necessarily represent irreversibly injured tissues, thus DWI/PWI mismatch does not represent pneumbra

Newer MR techniques are being developed to aid in the delineation of the dynamic pathophysiology of brain injury following ischemia. Novel MR sequences based on the BOLD mechanism are useful in the assessment of the extent of deoxygenation in ischemic tissue an adjacent areas to derive the oxygen extraction fraction (OEF). In addition, an absolute measurement of cerebral blood flow (CBF) can also be obtained. By combining both MR based CBF and OEF, metabolic rate for oxygen (CMRO2) may also be estimated.

Blood Oxygen-level dependent (BOLD) contrast

- Deoxyhemoglobin molecules behaves as paramagnetic particles which can induce local magnetic field changes.
- changes in the amount of deoxyhemoglobin will alter MR signal intensity in T2*-weighed images.

MR-CMRO2 = CBF x OEF

OEF = 1 - CBOS

From PET to MRI

- Can oxygen metabolism be measures by MRI?
- Blood oxygen-level dependent (BOLD) contrast
  - Deoxyhemoglobin molecules behave as paramagnetic particles which can induce local magnetic field changes.
  - Changes in the amount of oxyhemoglobin will alter MR signal intensity in T2*-weighed images = BOLD contrast

MR-CMRO2

- Cerebral oxygen saturation can be obtained with MRI.
- Assuming that the arterial blood is fully saturated (100%), OEF can be obtained as 1- CBOS

MR-CMRO2=CBFxOEF

Using MR-CMRO2 method, significant difference between core lesions that are destined for infraction vs. penumbra with viable brain tissue can be differentiated. Further advances in the development of MR-CMRO2 may obviate the need of PET scanners to measure CBF, OEF, and CMRO2, and may permit serial imaging to delineate the dynamic pathophysiology of brain ischemia. These MR- derived parameters may also supplement DWI/PWI in predicting the fate of acute ischemic lesions.

MR_CMRO$_2$ feasibility study in acute stroke patients - conclusions

- MR_CMRO$_2$ maps may reveal the viability of ischemic brain tissue.
- MR_CMRO$_2$ could potentially be utilized to identify the ischemic pueumbra and individualize therapeutic windows.
- The experimentally measured CMRO$_2$ threshold needs to be further evaluated in a larger sample size.

The visualization of water diffusion anisotropy in CNS white matters has made diffusion tensor imaging (DTI) a promising tool for non-invasive *in vivo* neuronal fiber tract mapping. This technique has been applied in human and animal brains for neuronal fiber tracking in three dimensions. DTI may be used to assess the extent of myelin formation or degradation. It carries the potential for differentiation of demyelination from the axonal injury. The DTI method has been used to assess myelin abnormalities in mice with genetic defects in white matter integrity. DTI may also be applied to define white matter injury in ischemic brain or traumatized spinal cord. DTI has greater sensitivity than conventional MR sequences in identifying acute or chronic white matter lesions, and is likely to be useful in the future to monitor the resolution or progression of white matter lesions caused by ischemia, trauma, or chronic neurodegenerative diseases.

Diffusion weighed MR Imaging

- Sensitive to tissue pathology.
- Early detection: stroke and tumor.
- complication: diffusion anisotrophy $\rightarrow$ misrepresentation of anatomy
- Advantage: diffusion anisotriphy $\rightarrow$ Diffusion Tensor Imaging (DTI)
- DTI: White matter tract tracking & quantitative analysis of white matter pathophysiology.

White matter injury in inflammation

- Inflammatory/immune reactions in CNS have a predilection to cause WHITE MATTER lesions.
- Inflammatory cells (PMN's, macrophages/microglia, and astroglia) and inflammatory mediators may play a more important role in the secondary injury to white matter.

Is white matter affected in Alzheimer's Disease?

- Amyloid peptides are cytotoxic to oligodendrocytes.
- Subcortical white matter lesions are common among patients with AD or cerebral amyloid angiopathy.
- Cerebral conduction delay has been documented in AD patients.

References:

Lin W, Paczynski RP, Celik A, Kuppusamy K, Hsu CY, Powers WJ: Experimental hypoxic hypoxia: changes in R2* of brain parenchyma accurately reflect the combined effects of changes in arterial and cerebral venous oxygenation saturation. **Magn Reson Med** 39:474-481, 1998.

89. Lin W, Paczynski R, Celik A, Hsu CY, Powers WJ: Experimental hypoxemic hypoxia: effects of variation in hematocrit and MR T2*-weighted brain images. **J Cereb Blood Flow Metab** 18:1018-1021, 1998.

Lin W, Venkatesan R, Gurleyik K, He YY, Powers WJ, Hsu CY: An absolute measurement of brain water content using magnetic resonance imaging in two focal cerebral ischemic rat models. **J Cereb Blood Flow Metab** 20:37-44, 2000.

Xu J, Chen SW, Ahmed SH, Chen H, Ku G, Goldberg MP, Hsu CY: Amyloid-β peptides are cytotoxic to oligodendrocytes. **J Neurosci** 21:RC118:1-5, 2001.

Chung Y. Hsu, M.D., Ph.D. is Elliot H. Stein Professor and Head, Cerebrovascular Disease Section, Department of Neurology, Washington University School of Medicine, and Director, Stroke Center, Barnes-Jewish Hospital, St. Louis, MO 63110