High-Resolution 31P Chemical Shift Imaging of Acute Stroke at 11.7T

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Introduction Ischemic stroke occurs when cerebral blood flow (CBF) drops below a critical threshold, resulting in energy failure. In vivo 31P chemical shift imaging (CSI) allows direct measurements of the high energy phosphates: adenosine triphosphate (ATP), phosphocreatine (PCr), and inorganic phosphorus (Pi). 31P NMR has proven useful for investigating the bioenergetics in normal brain (1). However, the low SNR, lengthy scan time and low spatial resolution of 31P NMR has prevented its widespread use, particularly in acute stroke studies.

In this study, we implemented and optimized 31P CSI on rat brain with reasonably high spatio-temporal resolution (0.94x0.94x6mm, in 15 mins), made possible with high field (11.7 T) and a double-tuned surface coil. This approach was used to investigate changes in high energy phosphates in acute stroke following permanent middle cerebral arterial occlusion (MCAO) in rats. In addition to 31P CSI, 1H diffusion, perfusion and T2 MRI were also acquired in the same animals to determine the spatio-temporal progression perfusion-diffusion mismatch and final infarct.

Methods Permanent MCAO was induced on male rats (200-250 g, n = 4) under 2% isoflurane during surgery (2). O2 saturation, rectal temperature and breath rate were monitored continuously and maintained at normal physiological levels. After surgery, isoflurane was reduced to ~1% and the animal was placed in the scanner.

MRI was performed on an 11.7T Bruker Biospin Magnet using a double tuneable (500/202.5 MHz) 2-cm diameter surface coil and 77 G/cm gradient insert. Quantitative 1H diffusion, perfusion, T2 MRI and 31P CSI were acquired. Anatomical (RARE) images were acquired with TR = 2 s, 8 echo trains, TEeffective= 65 ms, matrix = 128x128, FOV = 3x3cm², six 1.5-mm slices and 4 averages. ADC(trace) was measured using spin-echo EPI with matrix=96x96, FOV = 3x3 cm², and six 1.5-mm slices, TE=40ms, TR=1.5s, b = 5, and 3 directions of 1200 s/mm². CBF was measured using the continuous arterial spin-labeling technique with, single-shot, gradient-echo EPI, with parameters similar to the ADC measurement except TE=10.8ms, and TR=2s and 60 pairs of images. 31P CSI were acquired using FOV=3x3cm, matrix=5x5 (reconstructed to 32x32), spectral width = 50kHz, acquisition time = 20.48 ms, and 12.5kHz Bloch-Purcell RF pulse, 6 mm slice thickness. The 1H protocol took 12 mins and the 31P protocol took 15 mins. The entire 1H/31P protocol was repeated at 1 and 3 hrs after stroke and again at 24 hours.

ADC, CBF and T2 data were analyzed as described in (2). Two ROI’s containing mismatch and ischemic core and their homologous regions in the normal hemisphere were derived from the 30-min data set. 31P CSI analysis utilized Bruker software to overlay 31P color map on 1H image. Peak amplitudes were quantified. Radii of LH:RH for the mismatch and ischemic core ROI were analyzed.

Results Figure 1 shows a data set of ADC and CBF maps at 1hr after stroke and T2 map at 24 hrs after stroke. At the acute phase, the perfusion lesion was larger than the ADC lesion. At 24 hrs, T2 lesion became apparent and coincided with the perfusion deficit.

Figure 2 shows the 31P CSI for Pi, PDE, PCr, γ−ATP and total 31P signals (0.94x0.94x6mm) at 1, 3 and 24 hrs. At 1 hr after stroke, PCr and ATP in the core decreased markedly relative to the control hemisphere. In the mismatch region, PCr and ATP decreased less severely. Phosphodiesters (PDE) – a metabolite involved in oxidative damage – in contrast, was higher in the core than in control hemisphere. At 24 hrs after stroke, PCr and ATP decreased further and PDE increased further compared to earlier time points.

Figure 3 shows a 31P spectrum from 9 CSI voxels in the normal hemisphere and the ischemic core 1 hr after stroke, depicting dramatic losses of ATP and PCr in the ischemic core, albeit some partial volume effects.

Discussion This study demonstrates high spatiotemporal resolution 31P CSI can be used to measure changes of cerebral energy metabolites associated with acute stroke. High SNR was achieved using high magnetic field and a surface coil. Although partial volume effect exists, 31P CSI appears adequate to track the spatiotemporal progression of acute stroke changes in rats. Future improvement in 31P CSI spatiotemporal resolution is expected.

While the perfusion-diffusion mismatch has been used to estimate the ischemic penumbra, the mismatch’s ability to predict ischemic tissue fate remains controversial. A better marker for reversible and irreversible injury associated with acute ischemic stroke is needed. Given that 31P NMR has the potential to identify tissue with preserved cellular metabolism – which better approximates the ischemic penumbra than the mismatch, it has the potential to help better distinguish reversibly and irreversibly injured brain.

No other commonly used clinical imaging protocols could provide similar potential to help better distinguish reversibly and irreversibly injured brain. While the perfusion-diffusion mismatch has been used to estimate the ischemic penumbra, the mismatch’s ability to predict ischemic tissue fate remains controversial. A better marker for reversible and irreversible injury associated with acute ischemic stroke is needed. Given that 31P NMR has the potential to identify tissue with preserved cellular metabolism – which better approximates the ischemic penumbra than the mismatch, it has the potential to help better distinguish reversibly and irreversibly injured brain.

Although spatial resolution of 31P CSI is high, it is lower than 1H and is thus susceptible to partial volume effect. Future studies will improve CSI sensitivity, spatiotemporal resolution and develop magnetization transfer experiments to investigate kinetics of 31P energy metabolism. With high fields and continuing advances in MRI technologies, high spatiotemporal resolution 31P CSI may become practical.