Serial Triple Quantum Sodium MRI During Non-Human Primate Focal Brain Ischemia

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ABSTRACT

Stroke is the third largest cause of mortality in the United States. Ischemia such as that in acute stroke causes impaired energy metabolism, disturbs the Na-K-ATPase, and interrupts the continuous pumping of sodium out of the cell. The result is an increasing intracellular sodium concentration (ISC) in ischemia.[1] Several reports have demonstrated that the triple quantum (TQ) sodium NMR signal from biological tissue arises primarily from the intracellular sodium.[2,3] Consequently, TQ sodium MRI may prove to be a useful non-invasive method for visualizing the increase in ISC that occurs in ischemia. In this study, we demonstrate serial TQ sodium MRI in a non-human primate model of focal brain ischemia.

METHODS

Data Acquisition: Sodium 3D triple quantum (TQ) MRI data and proton MRI data were acquired on a 3 Tesla whole body scanner (GEMS, Milwaukee, WI), using ^{23}Na and ^{1}H quadrature birdcage RF coils custom-built to fit the animals (AIRI, Cleveland, OH). The TQ sodium images were acquired using a modification of a twisted projection imaging (TPI) sequence[4] that implemented a three-pulse triple quantum coherence transfer filter, as presented by Hancu et al.,[1] with a preparation time of 3.0ms (total scan time was 18 minutes). The k-space encoding used a 214 shot TPI trajectory leading to 26 seconds per full k-space volume (TR = 120ms). Proton SPGR and MR angiogram data were also acquired. **Animal Model:** Focal brain ischemia was induced in pig-tail monkeys (*Maccaca nemestrina*, n=4) using the endovascular method developed in our lab by Jungreis et al.[5] This approach uses embolization coils to occlude the posterior cerebral artery (PCA) and a balloon catheter to occlude the bifurcation of the middle cerebral artery (MCA) on the right hemisphere of the animals (Figure 1, left). The animals were kept under anesthesia throughout the experiment using a fentanyl infusion. Temperature was maintained at 37°C, and blood pressure and exhaled gases were monitored continuously using an MR compatible monitor (MEDRAD, Indianola, PA). Finally, the animal's position within the magnet was maintained throughout the imaging session using a custom-built cradle.

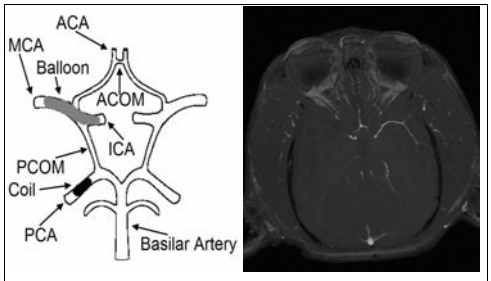

Figure 1: *Left: Diagram of the inferior view of the brain vasculature after endovascular occlusion, showing the positions of the balloon catheter (gray cylinder) in the right MCA and embolization coils (black cylinder) in the right PCA. Right: Proton MRA after endovascular occlusion of right PCA and MCA.*

RESULTS

The effectiveness of this model is shown in the right panel of Figure 1, where a proton MR angiogram (MRA) from a representative animal acquired after the endovascular occlusion of the right PCA and MCA is presented. The MRA clearly demonstrates blood flow in the MCA and PCA on the left side, but not on the right side of the brain. Figure 2 (left) shows selected partitions from three TQ sodium MR images acquired at 34 minutes (top row), 169 minutes (middle row), and 353 minutes (bottom row) after the endovascular occlusion, respectively. (Note that the balloon catheter in the right MCA was deflated and removed at 209 minutes resulting in partial reperfusion of the right MCA; therefore, the TQ image at the 353 minute time point was acquired 144 minutes after this event.) The TQ images were calibrated using sodium calibration standards within the field of view (40mM, 80mM, and 120mM NaCl in 10% agarose). The results show increased TQ sodium MRI intensity on the right side of the brain compared to the left side of the brain already at 34 minutes, but also at 169 and 353 minutes. In order to demonstrate the specific brain location of the TQ hyperintensity, registration of the TQ images with anatomical proton MR images and skull-stripping was performed. The middle panel of Figure 2 presents skull-stripped axial (top), coronal (middle), and sagittal (bottom) sections through the hyperintense region in the right MCA territory of the brain for the TQ sodium image (color) obtained at 169 minutes registered with an anatomical proton MR data set (grayscale). This again shows increased TQ intensity on the right side of the brain compared to the left at 169 minutes after endovascular occlusion. The two hyperintense regions on the axial section through this TQ image (in the right MCA and PCA regions) correspond to the areas on the MR angiogram (Figure 1, right) where the right MCA and PCA have been occluded. Figure 2 (right) shows a plot of the relative increase in TQ signal intensity on the right side of the brain (as % of contralateral signal intensity) for ROI's in the right MCA and PCA territories. Although there was TQ sodium MRI hyperintensity on the right side of the brain (relative to contralateral) at all three time points, the TQ relative change increased from the 34 minute time point to the 169 minute time point, and then decreased from the 169 minute time point to the 353 minute time point (which was 144 minutes after partial reperfusion of the right MCA). In fact, this decrease in the amount of TQ hyperintensity from 169 minutes to 353 minutes was greater for the MCA ROI than for the PCA ROI, which is consistent with the partial reperfusion of the MCA.

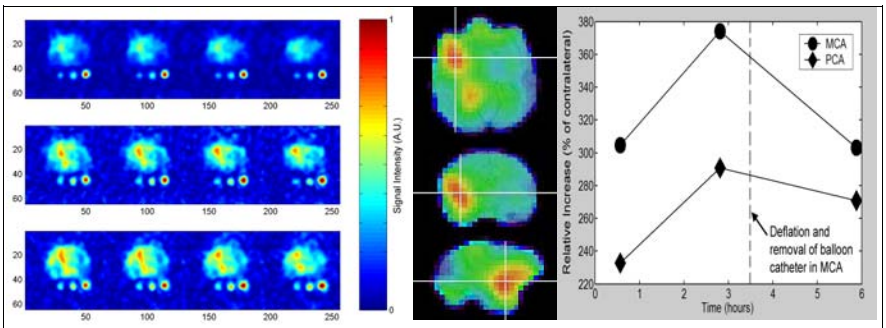

Figure 2: *Left column: Selected partitions from 3D TQ sodium images acquired at 34 (top row), 169 (middle row), and 353 (bottom row) minutes after the endovascular occlusion. Middle column: Skull-stripped axial (top), coronal (middle), and sagittal (bottom) brain sections through the hyperintense region in the right MCA territory for the 169 minute time point TQ sodium image (color) registered with an anatomical proton MR data set (grayscale). Right column: Plot of the relative increase in TQ signal intensity for ROI's in the right MCA and PCA territories compared to the contralateral side for the three different TQ sodium image time points.*

CONCLUSIONS

Triple quantum sodium MRI techniques have been demonstrated *in vivo* in a non-human primate model of focal brain ischemia. TQ sodium MRI hyperintensity was demonstrated in the ischemic hemisphere relative to the contralateral hemisphere as early as 34 minutes after the onset of ischemia. The TQ sodium MRI hyperintensity corresponded to the anatomical location of the ischemic cortex as indicated by the registration of the TQ image data with anatomical proton MR image data. No reports to date have demonstrated the presence of any contribution to the TQ sodium MR signal in the brain from the sodium in the extracellular compartment.[3] Because no reports have found any TQ contribution from the extracellular sodium, we believe that the TQ sodium MRI hyperintensity in the ischemic hemisphere is a result of the increase in the intracellular sodium concentration that occurs in ischemia.

REFERENCES

1) Hancu, I et al., Magn Res Med, **42**, 1146, 1999. 2) Seshan, V. et al., Magn Res Med, **38**, 821, 1997. 3) LaVerde, G.C. et al., ISMRM 13th Sci Meet, pp. 2483, 2005. 4) Boada, F.E. et al., Magn. Res. Med., **37**, 706, 1997. 5) Jungreis, C.A. et al., Am J Neuroradiol, **24**, 1834, 2003.

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