Serial Sodium MRI During Non-Human Primate Focal Brain Ischemia

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ABSTRACT

Sodium MRI has been implemented as an *in vivo* means for non-invasively visualizing the changes in tissue sodium concentration (TSC) that occur in ischemic tissue during acute stroke. In this study, we hypothesized that the rate of TSC increase can vary from subject to subject, and can also vary within the ischemic tissue of a single subject. To investigate this, we demonstrated the use of sodium MRI for measuring the time course of TSC in non-human primate focal brain ischemia.

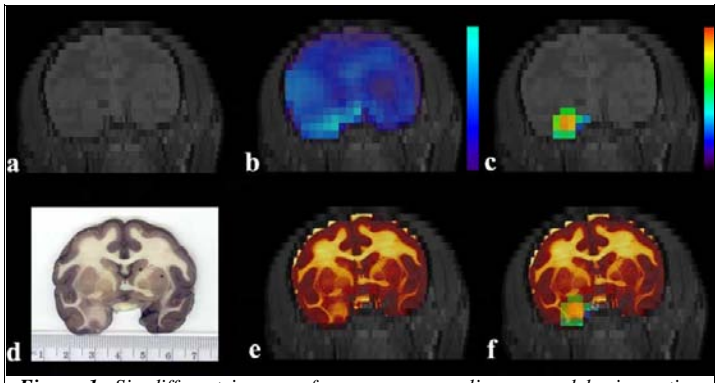


Figure 1: *Six different images of same corresponding coronal brain section (see "Results" section for details on images (a) through (f) and stroke region.*

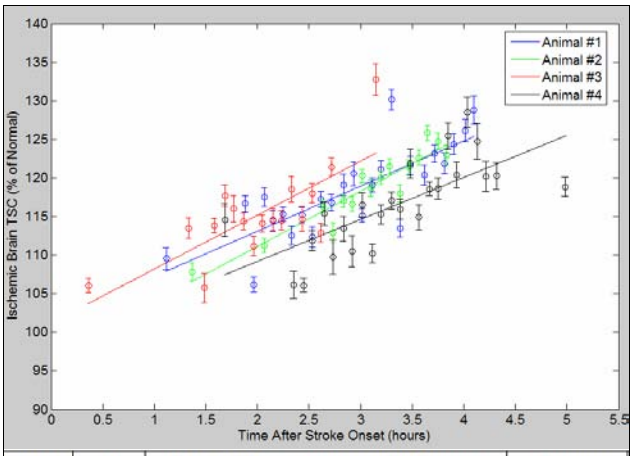
METHODS

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. (1). In this model, ischemia is achieved using embolization coils to occlude the right posterior cerebral artery (PCA) and a balloon catheter to occlude the right middle cerebral artery (MCA) at its origination from the circle of Willis. The animals were kept under anesthesia 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). The animal's position within the magnet was maintained throughout the imaging session using a custom-built cradle. Post mortem immunohistochemical staining with antibodies to microtubule associated protein 2 (MAP2) was also performed on the brains to identify the area of ischemic damage (2).

Data Acquisition: Sodium 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). Proton 3D spoiled gradient recalled echo (SPGR) and MR angiogram data were acquired. Single quantum (SQ) 3D sodium MR images were acquired throughout the duration of the experiment using a twisted projection imaging (TPI) sequence (3) with 816 scans, TE=0.5ms, TR=100ms, and NEX=4 for a total data acquisition time of 5.5 minutes. The arbitrary image intensities were then converted to TSC using sodium calibration standards within the image field of view. A minimum of 16 SQ sodium images were acquired during MCA occlusion. On a pixel by pixel basis the TSC is plotted versus time and a linear regression is performed to determine the slope of the TSC increase for that pixel (testing for a statistical significance of $p<0.05$). This results in a TSC slope map, which is an image in which the pixel intensity represents the slope of the TSC change over time for that pixel.

RESULTS

Figure 1 presents six different images of the same corresponding coronal brain section showing the stroke region in the inferior portion of the right hemisphere (left side of image). Figure 1 shows (a) the anatomical proton SPGR image for reference on which the images in (b), (c), (e), and (f) are then overlayed, (b) a skull-stripped SQ sodium image acquired 4 hours after stroke onset, (c) the TSC slope map calculated from 25 SQ sodium images acquired between 1 and 4 hours after stroke onset (d) the MAP2 immunostained histological section showing the infarct region indicated by decreased MAP2 immunostaining, (e) this same MAP2 immunostained section overlayed on (a), and (f) the TSC slope map overlayed on the MAP2 immunostained section. Figure 1 shows the agreement between the sodium MRI region with the highest rate of TSC increase and the infarct region demonstrated histologically by MAP2 immunostaining. Linear regression statistical analyses of the time courses of TSC in the ischemic brain (ROI indicated by the pixels identified on the TSC slope map) and normal brain were performed in all four animals (see Figure 2 bottom). As expected, in the normal brain (contralateral hemisphere) the TSC slope during MCA occlusion was not statistically different from zero in all four animals. The TSC in the ischemic brain (as percent of normal brain TSC) was found to have a statistically significant positive slope in all four animals ($p< 0.0006$) (see Figure 2 top and bottom). The regression line can be extrapolated to estimate the stroke onset time, and this can be compared to the actual stroke onset time. The time at which the linear regression of the ischemic brain TSC crosses 100% of normal is considered the error in the estimated stroke onset time.



Animal #	# of Sodium Images	Rate of TSC Increase During MCA Occlusion (%/hr ± 95% Confidence Interval)			Error in Estimated Stroke Onset Time (hrs)
		Normal Brain	Ischemic Brain	p-value	
1	25	0.52 ± 1.52	5.85 ± 1.97	3.00×10^{-7}	-0.235
2	16	-1.08 ± 1.20	7.15 ± 1.46	5.20×10^{-8}	0.449
3	17	-1.28 ± 1.67	6.99 ± 3.41	5.53×10^{-4}	-0.168
4	24	0.41 ± 2.29	5.44 ± 2.34	7.93×10^{-5}	0.317

Figure 2: *(Top) TSC data plotted versus time after stroke onset for the four animals (circles denote mean values and error bars denote ± standard error). The results of the linear regression analyses which found statistically significant positive slopes in all four animals are also shown. (Bottom): Table with results of linear regression statistical analyses of the time courses of TSC in the ischemic brain and the normal (contralateral) brain in the four animals.*

CONCLUSIONS

Sodium MRI has been implemented and investigated as an *in vivo* means for non-invasively visualizing the changes in TSC that occur in ischemic tissue during acute stroke. The results demonstrated that in each individual animal TSC increased linearly in the ischemic tissue during MCA occlusion, and that the rate of this TSC increase varied across the lesion. The slope of the mean TSC increase during MCA occlusion ranged from 5.44%/hr to 7.15%/hr across the four animals. This result was lower than the 16%/hour to 35%/hour reported for small animal models of focal brain ischemia (4, 5), presumably due to differences in cerebral metabolic rates between small animals and non-human primates.

The results also support the recent study by Jones et al. (5), which suggested that sodium MRI could predict the stroke onset time in patients that are unsure when their symptoms began, potentially increasing the number of patients eligible for thrombolytic therapy. In addition, our results support the thesis that using sodium MRI to measure the rates of TSC increase across the ischemic lesion could help make the clinical decision regarding thrombolytic therapy based on whether a significant volume of tissue has only seen mild increases in TSC.

REFERENCES

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