

The Quantification of Tissue Sodium Concentration using ^{23}Na -Magnetic Resonance Microscopy at 7 T: Probing the Acute Stroke Phase

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INTRODUCTION: Accurate identification of the potentially salvageable ischaemic penumbra is critical in identifying stroke patients who will benefit from thrombolysis and in designing future clinical trials of potential neuroprotectants. The perfusion/diffusion mismatch technique, currently used to detect penumbra is an indirect measure, lacking precision. The ability to accurately quantify TSC *in vivo* could allow developing of a direct bio-marker for tissue viability in stroke [1]. However, quantitative ^{23}Na -Magnetic Resonance Microscopy (qNa-MRM) of the rat brain is challenging due to the low SNR measured in the MRM images, which results from the ^{23}Na nucleus's low *in vivo* concentration, low gyromagnetic ratio, fast transversal signal decay, and the required small voxel size ($< 4 \mu\text{l}$).

METHODS: A $^{23}\text{Na}/^1\text{H}$ birdcage resonator with 72 mm inner diameter (i.d.) and a two-winding receive-only surface coil (i.d.: 20 and 30 mm) were developed to maximize B_1 -field homogeneity, SNR and acquire qNa-MRM images together with high resolution anatomical ^1H images. A 2D radial ultra-short TE (UTE) sequence on a Bruker BioSpec 70/30 system was used to achieve a short TE of 853 μs , with voxel resolution $0.78 \times 0.78 \times 2 \text{ mm}$, TR = 200 ms and 10 min acquisition time. The surface coil receive sensitivity profile was compensated using a reference phantom scan (Figure 1). The TSC quantification method was validated in test phantoms containing gels with various NaCl and agarose concentrations (40 – 160 mM, and 0 – 5 % respectively). The intraluminal thread model of middle cerebral artery occlusion (MCAO) was used to induce an experimental stroke, with the right MCA occluded in five male Sprague Dawley rats and sham surgical operation performed on a further two (bodyweights $320 \pm 21 \text{ g}$). The contralateral hemisphere served as a control during the experiment. ^{23}Na images were measured from as early as 26 min up to 8 h after MCAO. Physiology was kept stable during the imaging sessions by close monitoring of blood pressure, heart rate, temperature, and blood gases, following which the rats were sacrificed and the brains processed for histological analysis using haematoxylin and eosin staining. All experiments were carried out under appropriate animal license and ethics approval.

RESULTS and DISCUSSION: A quantified parametric map of the ^{23}Na concentration in the test phantom is presented in Figure 2, which also shows the close correlation between the set and quantified concentration values. Using these image acquisition parameters (i.e. voxel sizes of $1.2 \mu\text{l}$ acquired in 10 minutes), a quantification accuracy of $< 10 \text{ mM}$ was achieved, which enables the evolution of the TSC changes to be followed in the acute phase of a stroke. TSC maps for the *in vivo* study were computed and analyzed for each of the five stroke and two sham rats. The volume of irreversibly damaged tissue determined from the histology slices corresponded well with the tissue volume defined by elevated TSC values ($> 45 \text{ mM}$) at 8 h after MCAO. The TSC maps for one representative stroke rat are shown in Figure 3, presenting five coronal slices across the MCA territory at every hour for up to 8 h after MCAO. Clear increases in the TSC during this time period are evident in these maps, which further reveal regional variations in the TSC increase, for example between the caudate nucleus and cortex. Further analysis of the time-course of the TSC increase revealed delays in the time at which the TSC was observed to increase in these regions, with a rapid increase in the former and a delayed increase (by upwards of 2 hours post-MCAO) in the latter. A similar pattern of regionally-dependent temporal changes in affected tissue as determined from conventional ^1H T_2^* and perfusion weighted imaging after oxygen challenge in this stroke model was previously reported [2], however this has not previously been quantified using qNa-MRM. The ability to accurately measure such delay times in TSC increase using qNa-MRI, afforded for the first time by the current study, could enable the non-invasive determination of the irreversibly damaged tissue fraction of the ischaemic hemisphere. Such a direct and non-invasive marker does not currently exist.

CONCLUSIONS: The current study provides improved spatio-temporal resolution coupled with quantitative measures of TSC, allowing investigation of tissue fate in the acute stroke period. These results provide preliminary evidence that quantitative ^{23}Na Magnetic Resonance Imaging (qNa-MRI) may be capable of differentiating between viable and non-viable tissues in the human brain in the acute stroke period.

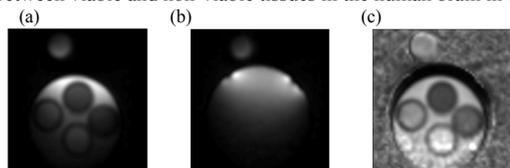


Figure 1: (a) The SNR map of a test phantom was divided by (b) the co-registered SNR map of a reference phantom to compute (c) the sensitivity corrected quotient image.

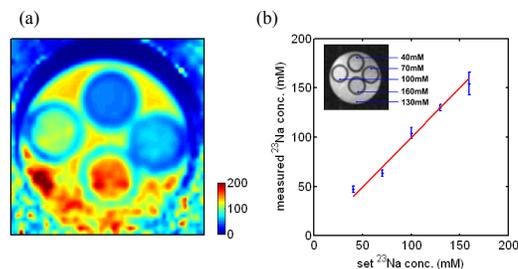


Figure 2: (a) Quantitative ^{23}Na concentration map of a test phantom (color bar in units of mM). (b) The quantified ^{23}Na concentrations as a function of set ^{23}Na concentrations, illustrating good linearity across the physiological and pathophysiological relevant range of ^{23}Na concentrations.

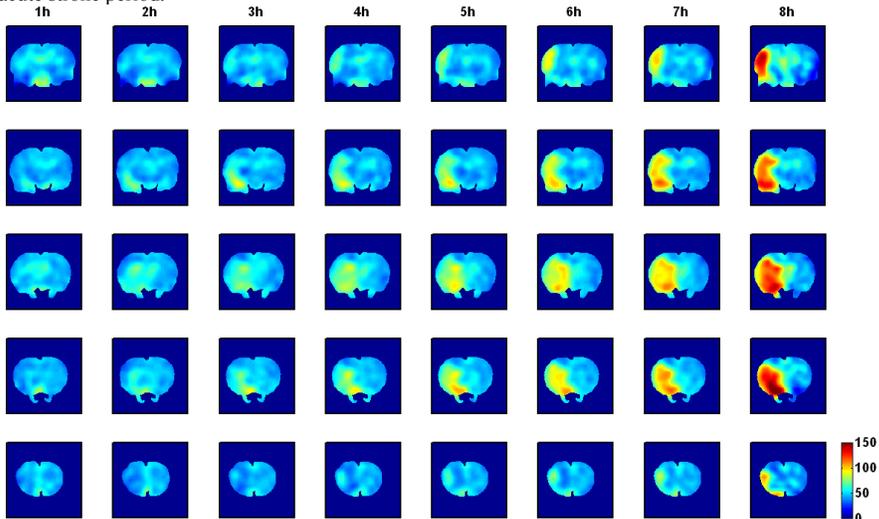


Figure 3: The evolution of TSC after MCAO for 5 coronal slices across 8 hrs in one representative brain. Times after MCAO are labeled above each column and the color bar indicates TSC in units of mM. Note the TSC changes in the ischaemic right hemisphere (left side on these TSC maps) after MCAO. Also note the delayed TSC increase in the cortex compared to the caudate nucleus.

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