Temporal water mobility and sodium intensity measurements in penumbra and core tissue during acute stroke

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INTRODUCTION: The perfusion-diffusion mismatch is a commonly used approach to distinguish between still-viable penumbra and irreversibly damaged core tissue in human stroke patients. However, in recent years it has become clear that the diffusion lesion does not accurately identify infarcted tissue, casting doubt on the validity of the perfusion-diffusion mismatch approach. Sodium-MRI (Na-MRI) can offer an alternative approach to identifying tissue at risk of infarction. The aim of this study was to investigate the hypothesis that an increase in ^{23}Na signal above normal levels indicates tissue destined for infarction [1]. To do this, the timecourse evolution of Apparent Diffusion Coefficient (ADC) and ^{23}Na signal changes during the acute phase of a rodent stroke model was measured, differentiating between penumbral and core tissue through the use of both the perfusion deficit measured immediately before the animals were sacrificed (~5hrs after stroke) and the subsequent histologically-determined regions of infarcted tissue.

METHODS: A home-built two-winding double-tuned ^{23}Na/^{1}H surface coil (i.d.: 20 and 30 mm) was used to allow for interleaved ^{1}H ADC and ^{23}Na measurements without the need to change coil systems during the experiment. ^{23}Na images were acquired using a 3D FLASH sequence on a 7T system (BioSpec, Bruker Biospin GmbH, Germany), with: TR/TE=20/2.1ms, 10% partial echo acquisition, BW=4kHz, voxel resolution (after two-fold 3D zerofilling) = 0.5x0.5x2mm^3, 5 minute acquisition. ^{1}H DWI images were acquired using an EPI sequence with TR/TE=4000/32ms, b=600s/mm^2, voxel size 0.25x0.25x1.9mm^3, 8 slices with 0.1mm gap, 8.5 minute acquisition. ^{1}H PWI images were also acquired prior to the rats' sacrifice by swopping the ^{23}Na coil system with a standard dual resonator system (72mm i.d. linear volume resonator and 20mm i.d. receive-only surface coil) in a continuous arterial spin labelling (CASL) EPI-based experiment, with: TR/TI/TE/TA=12000/2000/50ms/2min, in-plane resolution 0.26x0.26mm^2 for a single slice with 2mm slice thickness. All experiments were carried out under appropriate animal license and with institutional ethics approval. Stroke was induced by right middle cerebral artery occlusion (MCAO) in male Sprague Dawley rats (bodyweights ~300g, n = 6) using the intraluminal thread model. ^{23}Na images were measured from as early as 20 minutes up to 5 hours after MCAO, with ADC measurements performed in between. Blood pressure, heart rate, body temperature, and respiration were monitored and maintained within normal limits. Animals were killed by transcardial perfusion fixation using 4 % paraformaldehyde in phosphate buffer. Following fixation, brains were harvested, processed, and embedded in paraffin wax and subsequently sectioned at 6 µm and stained with haematoxylin and eosin for histological analysis. At ~5hrs after stroke core tissue was defined as regions of infarction identified in the histology slides, while penumbra tissue was defined as the mismatch between regions of perfusion deficit and core tissue. Regions of interest (ROI) were manually drawn in penumbra and core tissue in the ^{23}Na images and ADC maps. Mirror image ROIs were placed in identical anatomical locations of the contralateral hemisphere, to allow for relative comparisons of stroked-to-normal tissue signal levels.

RESULTS: The relative ^{23}Na images and quantitative ADC maps at different timepoints after stroke for one particular rat are shown in Figure 1. The relative perfusion map and histology line diagram delineating the region of infarcted tissue are presented in Figure 2. At the time of sacrifice, the tissue damage revealed by histology was confined to the subcortex for n=3 rats (core volume = 157 ± 37 mm³) and extended also into the cortex for the remaining n=3 (core volume = 318 ± 33 mm³). However, the perfusion deficit was found to extend into cortex for all six rats. Further, the area of significantly-increased (i.e. above the contralateral side) ^{23}Na signal closely matched the area of infarcted tissue in each rat. The ROI analysis for both relative ADC and ^{23}Na values is presented in Figure 3, showing data averaged across all six rats, where differences between the "core" and "penumbra" regions are clear in each case. The 30-minute gap between data points in the ^{23}Na time-series reflects the fact that ROIs in five consecutive 5-minute ^{23}Na images were averaged together for each data point. The large error bars, particularly in core tissue, reflect the variability in ^{23}Na signal increase in core tissue across the six rats. As found in previous studies [2], the ADC values experienced an initial decrease and remained relatively constant thereafter, with lower values in core compared to penumbral tissue. In contrast, the ^{23}Na signal did not remain constant over this period. Rather, the ^{23}Na signal increased steadily in both the core and penumbral tissue, albeit at different rates; while the former increased considerably relative to the contralateral side, the latter increased from an initial lower level to approximately equal that in the contralateral side at the end of the experiment for each rat. The fact that the first normalized data point in the "core" ROI was below one reflects that this ROI contained much still-viable tissue at the early timepoints.

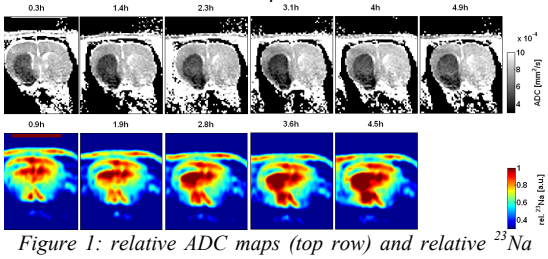

Figure 1: relative ADC maps (top row) and relative ^{23}Na images (bottom row) at specific time points post-stroke. The ^{23}Na signal was normalized to the mean signal value measured in a reference vial filled with 100mM NaCl, which was placed on top of the surface coil.

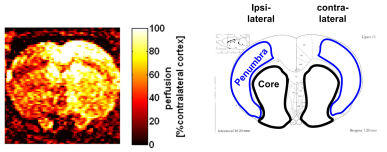

Figure 2: relative perfusion map in % (left) and corresponding histology line diagram (right) delineating ischaemic damage at 6 hours post stroke in a representative rat. Also included are the selected ROIs on the ipsi- and contralateral brain hemisphere for relative ADC and ^{23}Na measurements in penumbra and core tissue.

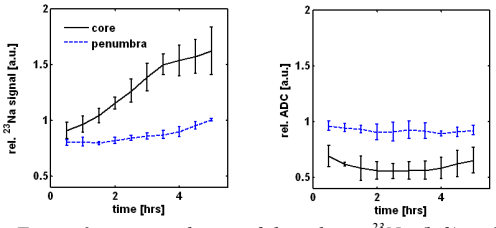

Figure 3: time evolution of the relative ^{23}Na (left) and relative ADC (right) for penumbra and core tissue after stroke. Data are presented as mean ± standard deviation.

DISCUSSION: Although both tissue regions exhibited an increase in ^{23}Na signal over the time period investigated, it should be noted that in the "ischaemic core" tissue ^{23}Na signal increased significantly above that on the contralateral side while the increase in the "penumbral" tissue ^{23}Na signal did not exceed that in the contralateral side. The fact that this "penumbral" tissue did not progress to infarct by the end of the experiment, as evidenced by the histology, supports the hypothesis that ^{23}Na signal below or equal to "normal" levels indicates still-viable tissue which, in this case, was nonetheless at risk of infarction given the perfusion deficit in this region. This contrasts with the behavior of the ADC values over this time period which, despite an initial decrease, predominately in the core regions, did not change appreciably. The results of this study suggest that a ^{23}Na-PWI mismatch may be a better approach to identifying penumbra and selecting patients who would benefit from a therapeutic intervention. Tissue regions exhibiting a perfusion deficit but with no ^{23}Na signal change or indeed a slight decrease could be used to confirm the presence of penumbral tissue, while tissue exhibiting an increase in ^{23}Na signal above normal levels could be considered to have already become irreversibly damaged.

CONCLUSIONS: For the first time, ADC and ^{23}Na signal changes in penumbra and core tissue have been measured during the acute phase of stroke in a rodent model. The data support the hypothesis that any increase in ^{23}Na signal above that of healthy tissue may indicate irreversibly damaged tissue, suggesting that a ^{23}Na-PWI mismatch approach could identify tissue at risk of infarction in the acute phase of a stroke.

REFERENCES: [1] Wetterling *et al*., Proc. ISMRM 18, Stockholm, 680 (2010); [2] Knight *et al*., Stroke 22, 802-808 (1991);

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