Comparison of apparent diffusion coefficient of water to histology in a model of hypoxia-ischemia in new-born brain

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Introduction: Diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) parameter mapping are relatively new methods for the clinical evaluation of infants who have suffered perinatal hypoxia-ischaemia (HI). These methods may delineate patterns of injury in the perinatal period before these patterns become apparent on conventional T_1 and T_2 weighted imaging [(1)], potentially elucidating a new 'window of opportunity' for therapeutic intervention. It has been shown that ADC decreases in the chronic phase following an HI insult correlate with secondary energy failure observed using ^{31}P spectroscopy [(2)]. The purpose of this study was to correlate changes in ADC with histology in a piglet model of cerebral HI.

Methods: Five new-born Large White piglets were studied before and after an acute HI cerebral insult; the durations of the experiments were 18, 30, 22, 48 and 48 hours post insult respectively. The insult was produced inside the spectrometer by reversibly occluding the carotid arteries by remote-control and reducing fractional inspired oxygen to 12%. This resulted in decreased phosphocreatine, [PCr], and adenosine tri-phosphate, [ATP] as assessed by continuous whole brain ^{31}P spectroscopy. Animals 1 and 2 were subjected to a 20 min insult whereas animals 3-5 had a more severe 50 min insult. MR data were acquired in a 7 Tesla Bruker Biospec spectrometer using a 6cm x 4cm elliptical surface coil positioned over the intact scalp in the crown position. A single axial imaging slice was selected so as to intersect the thalamus and the lateral ventricles. Single shot spin-echo diffusion weighted EPI (TE = 76ms; acquisition bandwidth = 200kHz; b = 0 and 817 s mm^{-2}) was used to obtain seven images from which the diffusion tensor was measured using a simplified methodology [(3)]. Parameter maps of trace ADC and lattice anisotropy were reconstructed. The anatomical information in these maps, was used to position regions of interest (RoIs) in the cortical grey matter at the top of the gyri and the base of the sulci in the areas denoted in figure 1. At the termination of the experiment, the intact brain was perfusion fixed with 4% paraformaldehyde and removed for histological analysis using hematoxylin and eosin stains. For regions corresponding to the defined RoIs, neurones were scored according to the following system: 0 – normal appearance; 1 – pyknosis (eosinophilic staining); 2 – mild to moderate shrinkage/deformation of the cell body/nucleus; 3 – same as 2 but with moderate to severe changes; 4 – acute neuronal death; 5 – entire neuronal loss. The percentage of neurones with each score within each region was recorded; endpoint ADC measures were then compared to the histology data. Counts of neurones which scored 0 or 1 were combined to give a percentage of normal or mildly effected neurones. Similarly, the counts of neurones that were scored as 4 or 5 were combined to give a percentage of neurones that were severely injured or dead. Neurones that were scored as either 2 or 3 contained a mix of populations that had potentially irreversible/reversible changes and were not considered further in this analysis.

Results:. At the point the experiment was terminated, animals 3, 4 and 5 showed large reductions in ADC in sagittal, para-sagittal and superior parietal regions (30 – 55% of baseline); in the inferior parietal region and in the temporal lobe the reduction in ADC was moderate (60 – 70 % of baseline). Animals 1 and 2 showed little or no ADC reduction in any area (92 – 110% of baseline). The evolution of ADC changes in representative cortical grey matter regions during SEF is shown in figure 2. The final ADC, expressed as a percentage of baseline, for all regions from all animals plotted against the percentage of neurones assessed as normal or only mildly affected is shown in figure 3. A similar plot showing final ADC plotted against the percentage of neurones that were severely injured or dead is shown in figure 4. Reduced ADC was seen to correlate to a small percentage of neurones having a normal appearance and to a large percentage of dead neurones ($p < 0.001$; Pearson product moment correlation).

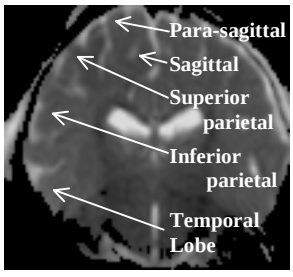

Figure 1: Anatomical regions

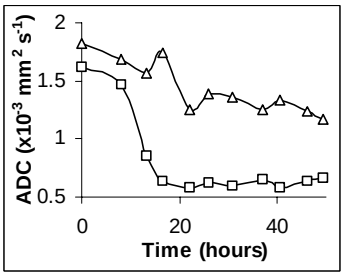

Figure 2: Plot of ADC vs time △ temporal lobe; □ Superior parietal

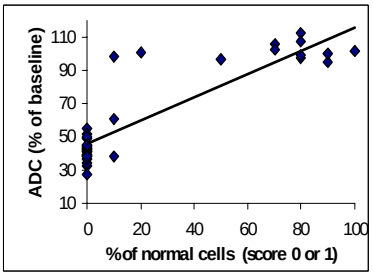

Figure 3: ADC change vs normal cell %

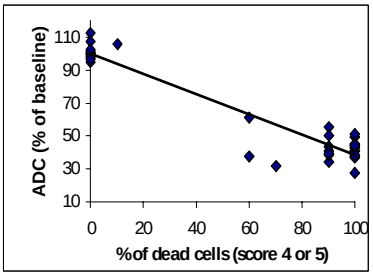

Figure 4: ADC change vs dead cell %

Discussion: These data show that a marked reduction in ADC during secondary energy failure correlates to large-scale neuronal death in this model of neonatal hypoxia-ischaemia. The two animals subjected to milder insults showed little or no decreases in ADC following the insult. Histologically there was no evidence of widespread neuronal death in these animals. However, the proportion of normal neurones varied greatly in areas where the measured ADC was 90-110% of baseline (figure 3). This suggests that mild-moderate histological changes in these areas were undetectable using ADC. These quantitative data support the findings of a previous study where hypo-intensity on ADC maps acquired from neonatal stroke patients correlated to areas of cytotoxic edema and neuronal death on histology [(4)]. However, the extent of damage was underestimated by the ADC maps. A rat model of adult stroke has demonstrated that up to 28% neuronal death may occur without any ADC change in the chronic phase post-insult [(5)]. Further investigations to correlate MR diffusion data with histology at early timepoints where the ADC changes have not fully evolved are planned.

References: [1] Barcovich AY *et al,* AJNR 2001; 32; 1786-1794. **[2]** Thornton JS *et al,* MRM 2001; 920-927. **[3]** Basser PJ & Pierpaoli C, MRM 1998; 39; 928-934. **[4]** Roelants-van Rijn AM *et al,* Neuropediatrics 2001; 32; 386-294. **[5]** Li *et al,* Stroke 2000; 31; 946-954.