Water Diffusional Kurtosis Imaging (DKI) Analysis of Ischemic Stroke Model in Juvenile Rats

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INTRODUCTION : Diffusional Kurtosis Imaging (DKI) is a clinically-accessible, NMR model of non-gaussian properties of water diffusion in tissue (considering b-factors up to 3000 s/mm²) [1]. Although based on a different hypothesis, the Statistical Model of Diffusion Imaging (SMDI) [2,3] is equivalent to the DKI model [1,2,3]. Although ischemic stroke has been studied extensively with gaussian diffusion models, it has only recently been shown in humans that the apparent kurtosis excess (K_{app}), that depend on the diffusion coefficients dispersion, increases in ischemic regions [5]. The excess Kurtosis of an unique water pool in a heterogeneous media is expected to be sensitive to both water restriction effects and exchange when varying diffusion time t_d [1, 3].

MATERIALS AND METHODS : *Stroke model* : 7 juvenile rats (7 days, ~20 g) were submitted to Middle Cerebral Artery Occlusion (MCAO) followed by a 2 h incubation in 8 % O_2, 92 % N_2 at 31-33°C**.** *NMR acquisition :* DWI-EPI images (357 µm x 312 µm, 6 averages, 10 slices of 1 mm thick, TE/TR=68/3200 ms) with diffusion gradients applied in R,S,P directions were acquired on a 4.7 T Brucker small animal scanner. A constant diffusion time (CT) Stejskal-Tanner MRI sequence was used with b-factors of 0, 500, 1000, 1500, 2000, 2500 s/mm² with a with diffusion gradient duration δ=4ms. Three different experiments were performed using gradient separation Δ=10,30,50 ms. *Post-Processing :* After registration and eddy-current correction, the direction independent S/S_0 pixel-by-pixel signal decay was interpolated to b-factors of 100, 200, 500, 750, 1000, 1500, 2000, and 2500 s/mm². After that, the S/S_0 images were non-linearly fitted by the medium b-values range simplified form of SMDI : $\mathbf{S/S_0=exp(-b.D_{app}+\frac{1}{6}b^2.\sigma^2)}$ [4,5]. K_{app} was computed as $\mathbf{K_{app}=3(\sigma^2/D_{app}^2)}$ [3,4,5]. *Statistical Analysis :* Cortical ROIs of healthy and ischemic areas, traced on D_{app} maps, were used as masks allowing the determination of D_{app} and K_{app} pixel-averaged spatial mean values, variances and histogram profiles. A non-parametric Kruskal-Wallis (rank sum) test, adapted for few-subjects study, was used to assess the statistical significance of the differences between ischemic and healthy tissue as well as the effects of diffusion time variations on pixel-averaged spatial mean, designed as $<D_{app}>$ and $<K_{app}>$.

RESULTS : For all diffusion gradient separation time (Δ=10,30,50 ms), the ischemic cortex is characterized by a reduction of $<D_{app}>$ (P=0.001745), and a rise of $<K_{app}>$ (P= 0.001745), when compared to healthy contralateral tissue, as illustrated by Fig. 1 and 2. Table 1 show the $<D_{app}>$ and $<K_{app}>$ values averaged for all rats studied. A reduction of 40 % for $<D_{app}>$ and a 55 % rise for $<K_{app}>$ were observed in the ischemic region compared to the healthy contralateral area. As shown in Fig 2., ischemic K_{app} values are more dispersed than normoxic K_{app}, ischemic D_{app} or normoxic D_{app} values. If D_{app} histograms in healthy versus diseased tissue were well separated (Fig 2, top), there is an overflow of the measured K_{app} values (Fig 2, bottom). No statistically significant differences were found (in both healthy and ischemic cortex) among $<D_{app}>$ and $<K_{app}>$ values obtained with the three different diffusion times.

Δ=10 ms	Healthy Cortex	Ischemic Cortex
$<D_{app}(cortex)>$	**1.415±0.1753 µm²/ms**	**0.8555±0.1987 µm²/ms**
$<K_{app}(cortex)>$	**0.5205±0.1159**	**1.105±0.2497**
Δ=30 ms	Healthy Cortex	Ischemic Cortex
$<D_{app}(cortex)>$	**1.395±0.1798 µm²/ms**	**0.7954±0.2345 µm²/ms**
$<K_{app}(cortex)>$	**0.4519±0.1264**	**1.011±0.2334**
Δ=50 ms	Healthy Cortex	Ischemic Cortex
$<D_{app}(cortex)>$	**1.5017±0.3058 µm²/ms**	**0.8966±0.2269 µm²/ms**
$<K_{app}(cortex)>$	**0.4520±0.1510**	**1.1012±0.3023**

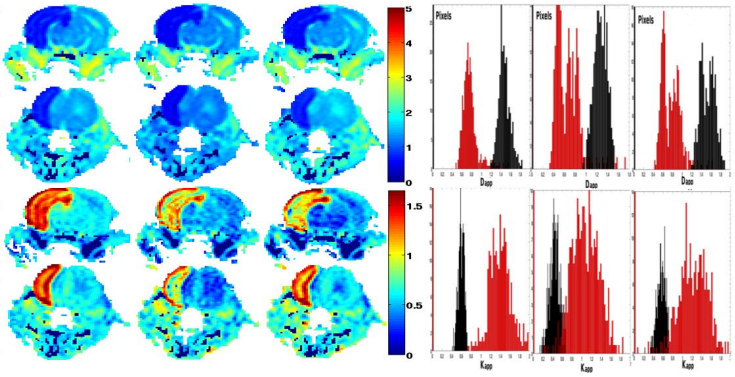

Table 1. Pixel-averaged intensity $<D_{app}>$ and $<K_{app}>$ values (given as mean ± total standard deviation) averaged over the 7 rats. Standard deviation include intra- and inter-subject dispersion around pixel mean value and subject mean value.
Fig. 1 (left). Parametric images of 2 non-contiguous slices of one rat 3h following MCAO. D_{app} (top) is displayed in µm²/ms, K_{app} (bottom) is dimensionless. **Fig. 2 (right).** Slices averaged histograms of D_{app} (top) and K_{app} (bottom) corresponding to Fig. 1 images, for healthy cortex (black) and ischemic lesion (red). For Fig. 1 and 2, images and histograms from left to right correspond respectively to Δ=10,30,50 ms.

DISCUSSION : For medium b-values, DKI and SMDI are equivalents models describing the non-gaussian diffusion of an unique water pool. Extending the fit to a complete SMDI model would possibly lead to the usability of a DKI-type model for b-values higher than 3000 s/mm² [2]. High K_{app} are representative of strong dispersion of mean diffusivities, reflecting the structural complexity of tissue [3]. As observed in humans [5], K_{app} is as sensitive as D_{app} (or equivalently, clinical ADC) in delineating the extent of ischemic region in the cortex. K_{app} also shows a spatial heterogeneity in the lesion compared to D_{app}. In this preliminary study performed in a limited number of subjects as well as with a limited diffusion times range, spatial averages $<D_{app}>$ and $<K_{app}>$ for healthy and ischemic parenchyma do not present any significant changes when varying diffusion times. Histological assessment of tissues properties in the stroke lesion is in progress and would confirm if K_{app} maps are able to differentiate internal tissue characteristics in the stroke lesion.

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