Influence of Brain Ischemia on Biexponential Water Diffusion MRI Signal Decay

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Introduction: Although DWI is routinely used in clinical practice for acute stroke detection, the biophysical and biological explanation of the physiological and pathological DWI contrast remain still unknow, because there is two or more « compartments » of water that did not match the respective volume and viscosity of the intra- and extra-cellular water [Niendorf, (1996)]. Despite that biexponential analysis is now a common diffusion analysis tool, there is actually no consensus to characterize the brain ischemic response with this model. Here we perform a biexponential analysis of one case of acute stroke, with the expectation that this model can lead to some anatomical informations about tissue microstructure. [Hakumaki, (2000)], in in vitro hippocampus slices have shown that cell osmotically-induced swelling is characterized by a change in the repartition of water pool fractions from $F_{(fast)}$ to $F_{(slow)}$ and that swelling associated with ATP-depletion in global hypoxia induce additionally $ADC_{(slow)}$ decrease. To our best knowledge, these important and specific $ADC_{(slow)}$ decrease have never been detected in human stroke.

Materials and Methods: DWI-EPI images (256x256x31) at constant diffusion time of a patient (4 days after acute stroke) were acquired with a clinical MRI scanner (Philips 3T Achieva). MR parameters used were TR/TE= 3179.5/70.5 ms, $b$ gradient factors $= [200,500,1000,2500 \text{ s/mm}^2]$ were applied in 3 orthogonal directions and averaged. Brain extraction, images registration and segmentation of the ischemic zone were realized with FSL with eddy-current distortion corrections. Hypothesis of biexponential (S/S0 = $F_{(fast)} \cdot \exp(-b \cdot ADC_{(fast)}) + F_{(slow)} \cdot \exp(-b \cdot ADC_{(slow)})$) for diffusion signal was considered as accurate in this b-value ranges and images of each parameters of the fit (minimized non linear least square residual) were extracted.

Results: Images resulting from the biexponential fit show mainly, in a restricted zone in the ischemic core compared to its contralateral counterpart, a huge rise for $F_{(slow)}$ and subsequent diminution of $F_{(fast)}$ associated with a slight decrease in $ADC_{(fast)}$ and a slight increase in $ADC_{(slow)}$ (Figure 1 D, C, A, B, Table 1). Mean changes in diffusion signal in ischemic (red) versus contralateral tissue (blue) is shown in Figure 2. Because of reduced clinical time (and reduced number of experimental points at high b-values) the estimation of $F_{(slow)}$ and $ADC_{(slow)}$ with this gradient configuration were probably the less accurate. However, one can see that the water fraction $F_{(slow)}$ found in our result has a T2 value similar to healthy tissue (Figure 1 F) as observed in FLAIR and RARE (T2) images, but give a strong DWI signal in the stroke zone (Figure 1 E).

### Table 1: Mean ± SE for all parameters of the biexponential fit for segmented ischemic and contralateral zone.

<table>
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<th>Contralateral zone</th>
<th>Ischemic zone</th>
<th>% changes</th>
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<tbody>
<tr>
<td>$ADC_{(fast)}$ (mm²/s)</td>
<td>$1.50 \times 10^{-3}$ ± $6.73 \times 10^{-5}$</td>
<td>$1.40 \times 10^{-2}$ ± $4.42 \times 10^{-5}$</td>
<td>-7.21 %</td>
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<tr>
<td>$ADC_{(slow)}$ (mm²/s)</td>
<td>$2.00 \times 10^{-3}$ ± $1.98 \times 10^{-6}$</td>
<td>$2.02 \times 10^{-3}$ ± $6.73 \times 10^{-6}$</td>
<td>+ 1.07 %</td>
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<tr>
<td>$F_{(fast)}$</td>
<td>0.68 ± 1.35 $10^{-3}$</td>
<td>0.46 ± 2.72 $10^{-3}$</td>
<td>-32.00 %</td>
</tr>
<tr>
<td>$F_{(slow)}$</td>
<td>0.27 ± 1.35 $10^{-3}$</td>
<td>0.49 ± 2.25 $10^{-3}$</td>
<td>+180.00 %</td>
</tr>
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Discussion: After cytotoxic edema, vasogenic edema (blood-brain barrier breakdown) occur, and changes in $ADC_{(slow)}$ progressively normalize, with an $ADC_{(fast)}$ increase and especially an $F_{(fast)}$ increase in the ischemic tissue [Brugières, (2004)]. These changes were not observed here. Global acute aglycemic hypoxia in hippocampus slices (40 min) has been shown to be characterized by an increase of $F_{(slow)}$ (17 % versus 25 % ) and a decrease of $ADC_{(slow)}$ (from $5\pm 0.5 \times 10^{-4}$ to 3.7± 0.4 $10^{-4}$ mm²/s), which seems to represent a specific hypoxic response because KCl-induced swelling cause only $F_{(slow)}$ increase with no $ADC_{(slow)}$ changes. Interestingly, this specific changes was not only ATP, but Ca$^{2+}$ or Mg$^{2+}$-dependant [Hakumaki, (2000)]. In the early work of Niendorf (1996), global ischemia in rats lead to same increase of $F_{(slow)}$, and same specific fall in $ADC_{(slow)}$ (1.68 ±0.10 versus 0.92 ± 0.06 $10^{-3}$ mm²/s) and fall in $ADC_{(fast)}$, that is never observed for cells in water medium. The $ADC_{(slow)}$ specific changes have never been described in focal ischemia in humans. Brugières (2004) have observed in an acute stroke intact zone a dramatic increase of $F_{(slow)}$ (26 % to 51 %) associated with an increased $ADC_{(slow)}$ (from $1.55 \times 10^{-4}$ to 2.24$10^{-4}$ mm²/s), with no significative $ADC_{(fast)}$ changes. We have observed the same type of result concerning $F_{(slow)}$ and $ADC_{(slow)}$ in this case of acute stroke before vasogenic edema, but, as Brugières (2004), we cannot characterize any decrease of $ADC_{(slow)}$ but only a small increase (with little experimental points), associated with the know characteristic rise of $F_{(slow)}$, interpreted as cell swelling.

![Figure 1](Image) Parametric images of $ADC_{(fast)}$: A (thresholded), $ADC_{(slow)}$: B (thresholded (mm²/s), $F_{(fast)}$: C, $F_{(slow)}$: D, b2500 image (UA): E, T2: F

Figure 2: Water diffusion biexponential signal decay: S/S0 = f(b). Red : mean signal of ischemic tissue. Blue : mean signal of contralateral tissue

References