

Local blood oxygen saturation and apparent water diffusion in acute ischemia

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Introduction

Therapy in acute ischemic stroke can only be effective in presence of salvageable tissue in the brain ischemic area. However, the ability to distinguish areas of non-salvageable tissue (ischemic core) from those of salvageable tissue (penumbra) remains a goal of diagnostic imaging in the selection of patients for thrombolysis. Recent evidence indicates that metabolic failure occurring after ischemia is critically dependent on residual cerebral blood volume provided by vasodilatation and recruitments of collaterals¹. Perfusion computed tomography is a quantitative widely used method in stroke patients that allows delineation of cerebral infarct². Magnetic resonance imaging (MRI), despite its higher brain sensibility, gives only qualitative perfusion information. Moreover, many observations reported that severe ADC decrease did not always reflect tissue infarction and thus limits its usefulness as a unique marker predicting infarction³. Thus, the aim of this study was to describe hemodynamic and oxygenation changes during acute cerebral ischemia using a multimodal quantitative BOLD approach (Apparent Diffusion Coefficient (ADC), Blood Volume fraction (BVf) and local Oxygen Saturation (ISO2)⁴).

Materials and Methods

Five Wistar rats underwent a focal cerebral ischemia by occlusion of the right middle cerebral artery (MCAo) and 4 rats were submitted to severe hypoxia ($\text{PaO}_2 = 40 \text{ mmHg}$). Rats were anaesthetized using isoflurane, ventilated and equipped with a catheter in the femoral vein to monitor hemoglobin, P_0_2 , PCO_2 and mean arterial blood pressure. MR experiments were performed at 4.7T (Bruker avance III console) using a volume / surface cross coil configuration. Blood volume fraction (BVf), apparent coefficient diffusion (ADC) and local blood oxygen saturation (ISO2) were measured once the MCA was occluded (Fig. 1A). All data were acquired with the same geometry (5 contiguous, 1mm-thick slices, $\text{FOV}=30 \times 30 \text{ mm}$; $\text{matrix}=64 \times 64$), except for B_0 mapping (3D GE sequence, $\text{FOV}=30 \times 30 \times 8 \text{ mm}$, $\text{matrix}=128 \times 128 \times 40$, $\text{TR}=100 \text{ ms}$ $\text{TEs}=4$ and 12 ms). Acquisition protocol was: brain shimming, ADC mapping ($b \sim 0$ and $b \sim 1000 \text{ s} \cdot \text{mm}^{-2}$ along three orthogonal directions), B_0 mapping, T_2 mapping ($\text{TR}=1500 \text{ ms}$, 20 spin-echoes, $\Delta \text{TE}=12 \text{ ms}$), T_2^* mapping ($\text{TR}=1500 \text{ ms}$, 30 gradient echoes, $\Delta \text{TE}=2.5 \text{ ms}$), BVf mapping (multiple gradient-echoes $\text{TR}=6000 \text{ ms}$; $\Delta \text{TE}=3 \text{ ms}$, before and 3min after injection of $200 \mu\text{mol/kg}$ of iron oxide particles (P904, Guerbet, France)). The entire MRI protocol lasted 25min per animal. Nominal spatial resolution was $470 \times 470 \times 1000 \mu\text{m}^3$. ADC was computed as the mean ADC across 3 orthogonal directions. BVf was computed from the change in T_2^* measured before and after injection of iron oxide particles (the change in blood magnetic susceptibility induced by the presence of the particles in the vasculature was set to 0.28 ppm^5). ISO2 was computed from the difference between $1/T_2$ and $1/T_2^*$ measured prior to iron oxide injection (using an hematocrit of 0.42 and a difference in magnetic susceptibility between fully oxygenated and fully deoxygenated hemoglobin of $\Delta X_0=0.264 \text{ ppm}^4$). Measures were performed in regions of interest (ROI) manually delineated on both ADC map (decreased ADC ROI and Contra ROI) and ISO2 map (Hypoxia ROI). Paired t-test was used for within-group comparison. A p value < 0.05 was considered as significant.

Results

Physiological parameters were not significantly different between rats (data not shown). The MRI session began 1 hour after the MCA occlusion enabling dynamic imaging of the acute phase of occlusion (Fig. 1A). One hour after occlusion, ADC values were lower in the decreased ADC ROI ($546 \pm 86 \mu\text{m}^2 \cdot \text{s}^{-1}$) than in the contralateral hemisphere (ADC=977 \pm 44 $\mu\text{m}^2 \cdot \text{s}^{-1}$) (Fig. 1B).

In the contralateral hemisphere, BVf and ISO2 were higher (BVf= $5.8 \pm 1.0\%$; ISO2= $86.3 \pm 3.9\%$) than normal values previously obtained in healthy rat brains (BVf= $3.4 \pm 0.4\%$; ISO2= $58.7 \pm 8.4\%$)⁴. The decreased ADC ROI was characterized by lower ADC, BVf and ISO2 values compared to the contralateral hemisphere ($546 \pm 86 \mu\text{m}^2 \cdot \text{s}^{-1}$, $3.1 \pm 0.5\%$, $57.0 \pm 3.9\%$, respectively; $p < 0.05$) (Fig. 1B). We observed a mismatch between the decreased ADC ROI defined on the ADC map and the hypoxia region delineated on the ISO2 map. The hypoxia ROI (ISO2= $33.3 \pm 2.3\%$) was smaller than the decreased ADC one. ADC and BVf values were similar both into the decreased ADC ROI and into the hypoxia ROI (546.5 ± 86.3 vs $559 \pm 9 \mu\text{m}^2 \cdot \text{s}^{-1}$; 3.1 ± 0.5 vs $2.1 \pm 0.5\%$) (Fig. 1B).

Discussion/Conclusion

To our knowledge, this is the first report of ISO2 MRI quantitative observations during the acute phase of MCA occlusion. This study supports the idea that ADC alone is not predictive from the non-salvageable tissue and must be associated with hemodynamic and oxygenation imaging. Our quantitative BOLD estimate of local blood oxygenation including BVf and ISO2 imaging could contribute to distinguish the ischemic core and the penumbra after cerebral ischemia. We identified the potential ischemic core as the region with low ADC and BVf values and with a severe hypoxia (ISO2 $< 35\%$) that is discrepant with tissue survival. We could discriminate the penumbra, where ADC values were also decreased but where BVf and a proper oxygenation were maintained, compatible with tissue salvation. With further investigations, our method could become a non irradiant and easily available way to investigate patients eligible for thrombolysis.

References : ¹Hossmann. Ann Neurol 1994; ²Wintermark et al. Stroke 2002; ³Fiehler et al. Stroke 2002; ⁴Christen et al. NMR In Biomed, 2010.

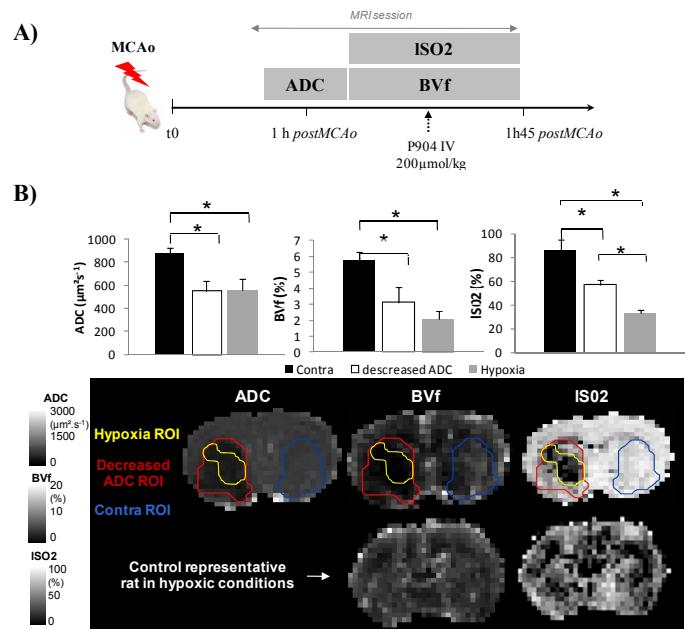


Figure 1. Quantification and mapping of ADC, BVf and ISO2 during acute cerebral ischemia

A) MRI protocol chronology (hours) from the end of surgery. B) **Top:** Quantitative analysis of ADC, BVf and ISO2 in the 3 regions of interest: contralateral hemisphere (contra, black); region of decreased ADC (decreased ADC, white) and hypoxia region (hypoxia, grey) (mean \pm SD). * $p < 0.05$. **Bottom:** ADC, BVf and ISO2 maps from a representative rat, with regions of interest (hypoxia ROI, yellow; decreased ADC ROI, red; contra ROI, blue). BVf and ISO2 maps from a representative rat submitted to severe hypoxia were submitted to severe hypoxia.