Quantification of local blood oxygen saturation by MRI to distinguish ischemic core from penumbra in experimental stroke

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Target audience: MR engineer, physicians and biologists interested by stroke

Introduction: Ischemic stroke is the leading cause of disability in adults, for which only one treatment is available, the thrombolysis. The eligibility of patients for reperfusion therapies depends on detection of a potentially salvageable tissue. Currently the most widely used clinical imaging modalities to detect the presence of penumbra is the mismatch between diffusion weight image (DWI)/perfusion weight image (PWI)[1]. However, many observations reported that diffusion abnormality did not always reflect tissue infarction and thus limits its usefulness as a unique marker predicting infarction [2,3]. Physiologic brain imaging to define tissue viability, brain perfusion, or metabolic status promises to improve patient selection for current therapies[4] or to avoid thrombolytic therapy in futile situations. The multiparametric quantitative blood oxygen level-dependent (mqBOLD) approach uses an analysis of the various contributions to the transverse relaxation time (T_2*) to obtain quantitative maps of cerebral oxygen saturation (SO_2)[5], which might allow a better distinction between non-salvageable tissue (ischemic core) from salvageable tissue (penumbra).

Purpose: The aims of this study are to evaluate the potencial of SO2 imaging to discriminate the ischemic core from the penumbra at acute phase; and to investigate which ischemic region measured at day 0 (D0) DWI or SO_2 MRI , is best correlated to the necrosis zone detected twenty one days after ischemia.

Methods: Male Sprague Dawley rats (Charles River, France), underwent transient focal brain ischemia induced by intraluminal occlusion of the right middle cerebral artery (MCAO). They were divided in 2 groups. In group 1, the rats (n=8) were imaged only at D0 (between 1 and 2 hours after MCAO) and euthanized two hours after pimonidazole administration. In group 2, the rats (n=10) were imaged at D0 and at day 21 (D21) after MCAO, and euthanized for histological analysis. MR experiments were performed on 4.7T (Bruker Avance III console) using a volume / surface cross coil configuration (IRMaGe facility). Blood volume fraction (BVf), apparent coefficient diffusion (ADC), cerebral blood flow (CBF) and tissue oxygen saturation (SO_2) were mapped. All data were acquired with the same geometry (5 contiguous, 0,8 mm-thick slices, FOV=30x30mm; matrix=128x128), except for B0 mapping (3D MGE sequence, FOV=30x30x8mm, matrix=256x256, TR=100ms TEs=4 and 12ms). Acquisition protocol was: T2w, ADC mapping (b~0 and b~=1000s.mm^{-2} along three orthogonal directions), B0 mapping, T_2 mapping , T_2* mapping, BVf mapping, (before and 1min after injection of 200µmol/kg of iron oxide particles (P904, Guerbet®, France)). The entire MRI protocol lasted 50min per animal. 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 0.28ppm [5]). SO_2 was computed from the difference between $1/T_2$ and $1/T_2$* measured prior to iron oxide injection (using a hematocrit of 0.42 and a difference in magnetic susceptibility between fully oxygenated and fully deoxygenated hemoglobin of ΔX_0 =0.264ppm). At D0, measures were performed in regions of interest (ROI) manually delineated on both ADC map (ROI "Edema" region of decreased ADC and ROI "Contra" contralateral striatum) and SO2 map ("Hypoxia" voxels with SO_2 <40%). A ROI "Mismatch" was defined as the in "Edema" ROI with SO_2 >40%). At D21, the measures were performed on the ADC map (ROI "Damaged Hemisphere" and ROI delayed necrosis by including voxels with increased ADC). Paired t-test was used for within-group comparison. A p value < 0.05 was considered as significant. Pearson correlation was performed to compare edema and hypoxic areas mesured at D0 with the necrotic areas mesured at D21 in the same animals.

Results: In group 1 (n=8) we observed at D0 a significant mismatch between "Edema"-ROI and "Hypoxia"-ROI which was always included in the "Edema"-ROI (102.5±5.31mm^3 vs 44.6±11.25mm^3) with similar ADC-reduction (contra: 841±43, edema: 576±52 ; mismatch: 590±47 and hypoxia: 565±55 µm²/s). In the "Mismatch"-ROI, we observed a similar ADC decrease but a higher CBF, BVf and SO2 (CBF 35.6±7 mg/100g/min; BVf=2.7±0.3 mL/100mL; SO_2=61.7±0.9%) than in "Edema"-ROI (CBF= 29.7±4 mg/100g/min; BVf= 1.8±0.4 mL/100mL; SO_2=42.7±4%) and "Hypoxia"-ROI (CBF=27.1±3 mg/100g/min; BVf=1.5±0.4 mL/100mL; SO_2=21.2±1.5%). On the 21 days follow-up (n=10) we observed a statistically significant difference between the region of necrosis at day 21 (21.12%) of ROI damaged hemisphere) and the region hypoxia (9.82%) at day 0 and a tendency with the ROI Edema (26.5%). Correlation were obtained between delayed necrosis and Edema (R^2= 0.96) and delayed necrosis and Hypoxia (R^2=0.92).

Discussion: A quantitative estimate of cerebral oxygen saturation is of critical importance in the investigation of cerebral diseases like stroke. In acute stroke, diffusion (ADC) overestimates the ischemic core size. Indeed ADC-decrease "lesion" includes some areas with an oxygenation level (lSO2>40%) allowing tissue survival. The follow-up study, showed that the hypoxic area measured on the SO_2 map underestimate the size of the delayed necrosis while the edema area measured on the ADC map at D0 tends to overestimate the delayed necrosis.

Conclusion: Quantification of local blood oxygenation by qBOLD-MRI can contribute to distinguish more accurately the ischemic core and penumbra. This approach may in the future be used as initial emergency imaging to assess infarction size and drive treatment such as trombolysis for acute stroke.

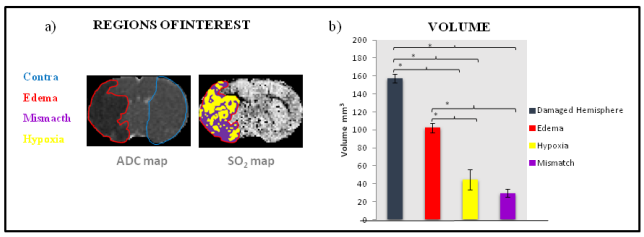

Figure (fig) 1: a) Regions of interest on the ADC and SO_2 map at D0; b) Surfaces of different regions of interest on the damaged hemisphere at D0.

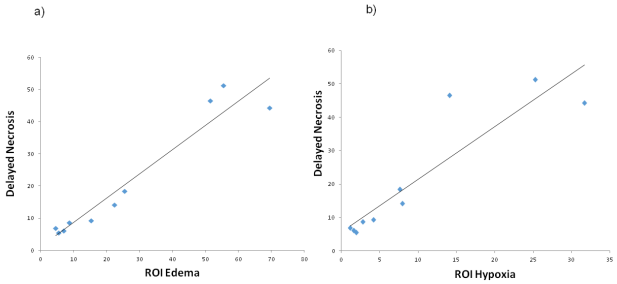

Figure 2: a) Correlation between the surfaces of decreased ADC (fig. **a** R^2= 0.96) or SO_2 (<40%) (fig.**b** R^2=0.92) at D0 and the region of necrosis final at D21 (% the number of pixels in the right hemisphere).

References: [1] Guadagno et al. Curr Opin Neurol 2004; [2] Fiehler et al. Stroke 2002; [3] Hossmann et al. Neuropharmacology. 2008; [4] Santosh et al; JCBFM. 2008, [5] Christen et al. JCBFM 2014.