New MRI contrasts in experimental stroke: What do we measure with RAFF and ZAPI?

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Introduction. MRI is a powerful diagnostic imaging modality of cerebral ischemia, and at the same time MRI provides handle to patho-physiological events of ischemic stroke, including drop in intracellular pH, altered mobility and structure of macromolecules (MM), water shift between intra- and extracellular space as well as net water accumulation. Each of these processes proceeds at different time course following stroke and contribute to MRI parameters [1,2]. In this work we have applied two novel MRI contrasts to study acute stoke in a rat model: (a) RAFF, Relaxation Along Fictitious Field [3] combines periods of $T_{1\rho}$ and $T_{2\rho}$ relaxation under an RF filed of varying phase and amplitude. Relaxation is influenced by both dipolar and exchange contributions which can be modeled using Bloch – McConnell equations [4]. The exchange processes that contribute to RAFF relaxation are ones occurring near the average RAFF RF amplitude, typically a few hundred Hz. (b) ZAPI, Z-spectroscopy using Alternating Phase Irradiation [5], provides a tool for on-resonance MT and control of the MM T_2-distribution contributing to MT, so called T_2 filter. Our aim is two-fold: to examine the sensitivity of the novel MRI techniques to acute stroke, and to use these MRI techniques to assess evolution of different physico-chemical processes in acute stroke.

Methods: Ischemia was induced by middle cerebral artery occlusion (MCAO) in Wistar rats (n=9), sham operated rats (n=2) were used as controls. Temperature and blood gases of the animals were monitored during the experiments. Imaging was performed at 4.7 T (Varian Unity Inova, quadrature transmit/surface receive RF coils, Rapid Biomedical) under isoflurane anesthesia. Relaxation times were mapped as follows: T: adiabatic double echo, TE10-80 ms, TR 2.5s. $T_{1\rho}$: TSL 8-64 ms TR 2.5 s, AHP-CW-AHP spin lock of amplitude 1500 Hz. RAFF: pulse train 0-144 ms with peak RF amplitude 625 Hz. $D_{av}$was measured to assess tissue status: 4 b-values 0-1370 s/mm^2. For MT, constant-phase (CP) and ZAPI-MT were acquired: 7 s irradiation with 50 Hz rms. amplitude, offsets 25 and 50 ppm (CP) and 0 ppm (ZAPI, sinusoidal modulation, τ=100,80,60,40 µs), reference at 250 ppm (both), TR 12 s. All data were acquired using FSE readout (8 echoes, 10 ms apart, 128x 64, 25.6 x 25.6 mm^2, 1 mm slice). All MT data were normalized to the reference image. T_2-filtering in ZAPI at given τ was evaluated as S(τ =100 µs)/S(τ), where S in the normalized ZAPI signal. The non-steady state model [4] with $T_{1\rho}$ and $T_{2\rho}$ relaxation values and exchange parameters from a previous work [6] was used to simulate RAFF change between time points of 120 min and 230 min. All presented data are ROI averages from ten brain regions (bilaterally, Fig.1).

Results and discussion: On average, D_{av} had decreased by 42 % by 100 min of MCAO, indicating severe ischemia in all brain regions studied. T_1 was significantly elevated in all brain areas at all time points and increased steadily throughout the MCAO. Early T_2 showed BOLD-related decrease [7], followed by a time-dependent steady increase, with delayed onset in cortical areas. MT was significantly increased in ischemic regions (Table 1) but remained invariant of time. The time course of RAFF signal was similar to T_2, reflecting sensitivity to processes with relatively long correlation times, but strikingly different from that of MT. Simulations of RAFF signal predicted the measured increase in RAFF accurately. MT acquired with offset-CP irradiation showed higher MT and stronger response than on-resonance ZAPI, possibly reflecting additional contribution of direct saturation of water in the former method. Significant differences in ZAPI signal collected with different τs (T_2-filtered MT, Table 1) were seen in early stroke, suggesting alterations in MM T_2 distribution. Both ZAPI and RAFF may be influenced by B_1 inhomogeneity, however, in sham-operated animals no systematic differences in B_1 between the hemispheres were detected indicating that the effect of negligible B_1 inhomogeneity.

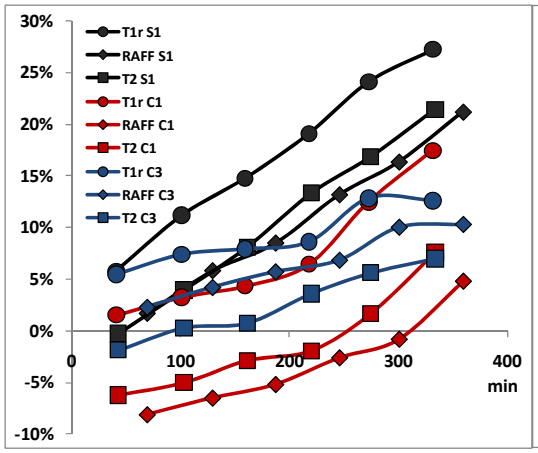

Fig. 2: Relaxation: changes (ipsi-contra)/contra during evolution of stroke in three brain regions (S1, C1 and C3, see Fig. 1)

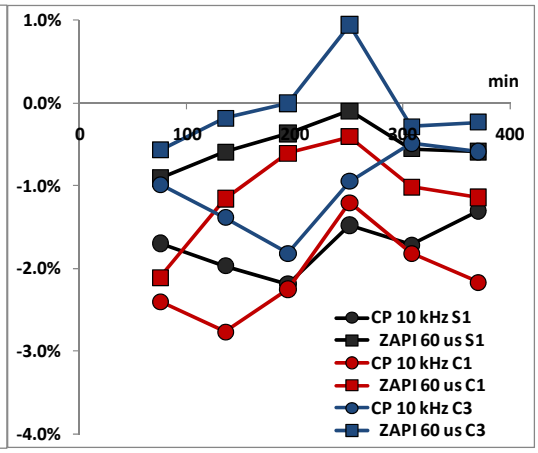

Fig. 3: MT: relative changes in CP and ZAPI-MT

Timep.	RAFF	CP 10kHz	ZAPI 60µs	T_2Filt. 60 µs
S1 # 1	0.15	**0.02**	**0.03**	**0.03**
# 2	**0.00**	**0.00**	0.09	0.44
# 3	**0.00**	**0.00**	0.19	0.17
# 4	**0.00**	**0.02**	0.43	0.28
# 5	**0.00**	**0.04**	0.06	0.43
# 6	**0.00**	0.08	0.19	**0.05**
C1 # 1	**0.01**	**0.02**	**0.00**	**0.03**
# 2	**0.01**	**0.00**	0.08	0.21
# 3	**0.03**	**0.00**	0.08	**0.03**
# 4	0.16	**0.04**	0.34	0.49
# 5	0.39	**0.03**	**0.02**	0.11
# 6	0.07	**0.03**	0.37	0.43

Table 1: T-test results, $p < 0.05$ in green

Conclusions: The following conclusions are drawn: 1) Relaxation and MT are not coupled in acute cerebral stroke, even when clean ZAPI MT is used, indicating that MT effect on the relaxation times quantified is small. 2) RAFF signal is sensitive to ischemia with sensitivity and temporal behavior comparable to T_2, but inferior to $T_{1\rho}$. 3) RAFF signal change in ischemic tissue can be predicted by simulations. 4) On resonance-MT differs from off-resonance MT, both in magnitude and in temporal evolution during stroke.

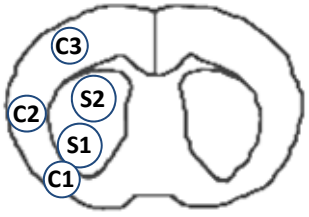

Fig. 1: The ROI locations

References: [1] Hoehn-Berlage M. et al. MRM 1995 Dec;34(6):824; [2] Jokivarsi et al. Stroke 2010 41(10):2335; [3] Liimatainen et al. MRM 2010 64(4):983; [4] Liimatainen et al. Proc. ENC 2009; [5] Närväinen et al. JMR 2010 in press; [6] Jokivarsi et al. JCBFM 2009 29(1):206; [7] Gröhn et al. JCBFM 2000 20:316

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