Simultaneous Imaging of Absolute CBF Change and BOLD with Saturation-Recovery-T1 MRI Approach under Ischemia and Hypercapnia

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Introduction: Measurement of cerebral blood flow (CBF) provides important information related to brain physiology, function and viability. It is known that T_1 relaxation processing is sensitive to cerebral perfusion. Thus, CBF can be imaged by MR-based arterial spin labeling (ASL) techniques[1-5]. ASL techniques usually acquire paired images: one control and another with spin tagging, with a relatively long inversion recovery time, thus, long repetition time (TR). These MR-based CBF imaging methods are useful for mapping the relative CBF changes caused by physiological/pathological perturbation, but less robust for quantifying the absolute CBF change due to the requirement of more physiological parameters and complexity of blood circulation in a living brain. In this study, we proposed a simple approach based on the saturation-recovery T_1 imaging method for simultaneously measuring absolute CBF change and BOLD. This approach was tested by examining the quantitative relationship between the absolute CBF changes based on the approach and the simultaneously measured CBF using laser Doppler flow (LDF) recording under ischemia and hypercapnia conditions in the rat brains.

Theory: The proposed method relies on T_1 mapping using the saturation-recovery preparation and fast EPI sampling. The water saturation preparation was achieved by the use of a global adiabatic 90° excitation pulse followed by dephasing gradients for nulling the longitudinal water magnetization. A number of measurements with varied saturation-recovery time (T_{SR}) were performed without an extra waiting delay among these measurements due to the fact that the initial magnetization of water spin after the saturation preparation is always zero and independent upon TR. The longest T_{SR} of ≥ 4 times of apparent T_1 of brain tissue (T_1^{app}) was applied in this study to: i) improve the reliability of T_1 exponential regression, and ii) measure the true BOLD contrast without any contaminations from perfusion. The apparent T_1 relaxation rate ($R_1^{app}=1/T_1^{app}$) can link to CBF according to: $R_1^{app} \approx R_1^{int} + R_1^{temp}+CBF/\lambda$, where R_1^{int} is the intrinsic R_1 of tissue water and is commonly insensitive to physiology change and can be treated as a constant; R_1^{temp} reflects the R_1 process related to brain tissue temperature change; λ (=0.9ml/g) is the blood-tissue water partition coefficient. The difference of R_1^{app} values measured during control condition and after physiological perturbation becomes: $\Delta R_1^{app}=\Delta R_1^{temp}+\Delta CBF/\lambda$; or $\Delta CBF = \lambda(\Delta R_1^{app} - \Delta R_1^{temp}) = \lambda \Delta R_1^{CBF}$, where ΔR_1^{CBF} is determined by CBF change. In this study, the saturation-recovery T_1 imaging method combined with EPI acquisition was applied to: i) measure ΔR_1^{app} resulting from either acute ischemia (CBF suppression) or hypercapnia (CBF increase) compared to the control condition, and ii) determine the relationship between brain temperature and R_1^{temp} measured after complete cardiac arrest (i.e., CBF=0) with KCl bolus injection. Finally, we quantified the absolute ΔCBF as well as BOLD, and then compared ΔCBF with the relative CBF change (ΔCBF/CBF = rCBF) which was simultaneously measured by LDF.

Material and MRI method: Twelve male Sprague-Dawley rats weighing between 293 and 363 g were subjected to 1-minute acute global ischemia by using the four-arterial vessel occlusion model under 2% isoflurane anesthesia. The simultaneous MRI/LDF/temperature measurement was conducted in 5 rats. The OxyLab LDF/OxyFlo instrument (Oxford Optronix, UK) was used to measure the changes of both CBF and brain temperature in the rat cortex of one hemisphere (1.5-4 mm lateral, 1.5-3 mm posterior to the bregma, 1.9 mm deep). On three of these five animals we also performed a hypercapnia experiment (10% CO_2) for 7 minutes before ischemia. The first two minutes serve as control stage (S1), the following induced hypercapnia or ischemia is the second stage (S2). The post hypercapnia/ischemia divided into S3, S4 and S5 stages. The MRI experiments were carried out in a horizontal 9.4T animal magnet with an 8-shape surface coil (2.8×2 cm). Gradient echo EPI (TE=21ms; FOV=3.2×3.2cm; image matrix=64×64; single slice with 2 mm thickness) combined with the saturation recovery preparation was used for imaging T_1^{app} and T_1^{temp} with varied T_{SR} values of 0.004, 0.1, 0.2, 0.3, 0.4, 0.5 and 10 s resulting in a temporal T_1 imaging resolution of 11.9 s. Both ROI and single pixel data taken from the rat somatosensory cortex were used to perform the T_1 regression analysis and determine ΔR_1^{app} and/or ΔR_1^{temp}, and then ΔCBF according to the equations mentioned above. The absolute CBF value at control was further estimated from the measured ΔCBF and the corresponding rCBF measured by LDF under the ischemia condition. Perfusion and BOLD change maps were generated with two-dimensional median filtering on a pixel by pixel basis.

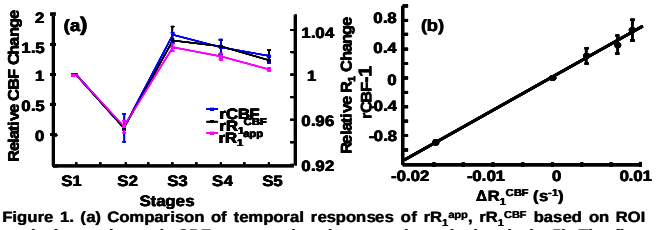

Figure 1. (a) Comparison of temporal responses of rR_1^{app}, rR_1^{CBF} based on ROI analysis results and rCBF measured under one-minute ischemia (n=5). The first data point on the left side represents the control stage (S1) and serves as a reference for normalization of other data points. The second data point stands for the averaged results measured under ischemia (i.e., Stage 2 or S2). The third, fourth and fifth data points present the measurement results during three post-perturbation stages (S3, S4 and S5). (b) Liner correlation between rCBF change and ΔR_1^{CBF}. The vertical lines indicate the standard error of mean (SEM).

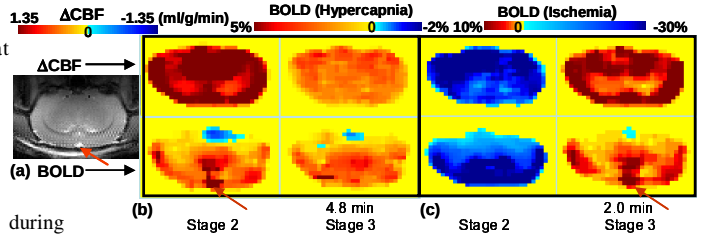

Figure 2 (a) Anatomic coronal image of a representative rat brain. ΔCBF and BOLD images obtained from (b) hypercapnia and (c) ischemia study, respectively, during Stages 2 to 3. The time indicated below is the image sampling time after the termination of Stage 2 (S2). The arrows point to the sinus vessel. The total image averaging times for Stages 2 to 3 (i.e., S2, S3) were: 2.5, 6.5 minutes for the hypercapnia study; and 1.0, 1.8 minutes for the ischemia study.

Results and discussion: The rat brain temperature increased 0.93±0.09ºC during hypercapnia (n=3) and decreased 0.26±0.02ºC during ischemia (n=5). The averaged temperature dependent T_1^{temp} factor was 36.1±8.7 (ms/ºC). During hypercapnia, ΔR_1^{CBF} increased 5.1±0.8% corresponding to 52.6%±13.4% increase of CBF measured by LDF and 4.5±2.7% BOLD effect compared with the control condition. In contrast, during ischemia, ΔR_1^{CBF} decreased 4.7±1.2% corresponding to 89.5±1.8% decrease of CBF and –23.1±2.8% BOLD effect. The temperature change in the brain cortex could account for the contribution of 15.3% and 3.2% to the measured T_1^{app} value under the hypercapnia and ischemia condition, respectively. Figure 1a shows excellent consistency of trends among the MRI-measured rR_1^{CBF}, rR_1^{app} and LDF-measured rCBF during ischemia and post-ischemia periods. However, rR_1^{CBF} has a better correlation with rCBF than rR_1^{app}. Figure 1b shows an excellent linear correlation between rCBF and ΔR_1^{CBF}. The absolute CBF increased 1.19±0.19ml/g/min during hypercapnia, and decreased 1.07±0.24 ml/g/min during ischemia. Furthermore, the estimated control CBF value (1.19±0.27 ml/g/min) is coincident with the literature values ranging from 1 to 1.5ml/g/min in the rat brain cortex under similar anesthetic condition. Figure 2 shows the ΔCBF and BOLD maps in a representative rat brain acquired during and after acute ischemia and hypercapnia perturbation respectively, suggesting excellent measurement reliability with a relatively short imaging acquisition time in the range of one or few minutes. The results clearly demonstrate that the ΔR_1^{CBF} image is sensitive to the CBF change. Although, the possible inflow effect on the measured ΔR_1^{CBF} value cannot be completely excluded in this study, the large-vessel inflow effect contribution is expected to be small. Our recent studies have shown that the substantial suppression of large vessel signals by using diffusion gradients with very high b factor could not significantly change the R_1^{app} value, suggesting that the inflow effect of large vessels might not play a crucial role in determining ΔR_1^{CBF} and ΔCBF. Furthermore, BOLD images show hot spots (indicated by red arrows in Fig 2.) because of the large BOLD effect near the sinus vein. In contrast, such hot spots were not observed in the ΔCBF maps, indicating again that the measured ΔCBF images are more specific to tissue perfusion and less sensitive to macro vessels. The overall results reveal that the proposed saturation-recovery T_1 MRI method should provide a robust, noninvasive neuroimaging tool for simultaneous imaging absolute CBF change and BOLD associated with brain physiology, function and viability.

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References: 1. Williams et al. *PNAS*, 1992; 2. Edelman et al. *Radiology*, 1994; 3. Kim, *MRM*, 1995; 4. Kwong et al. *MRM*, 1995; 5. Schwarzbauer et al. *MRM*, 1996.