Improved ^{31}P Saturation Transfer Approach for Imaging Cerebral ATP Metabolic Rates *In Vivo*

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INTRODUCTION The cerebral ATP metabolism plays a central role in neuroenergetics for supporting brain energy and function and it is regulated by the three-site chemically exchange system of Pi↔ATP↔PCr for maintaining a stable ATP content in the brain. Recent progress has demonstrated that the use of *in vivo* ^{31}P MRS combined with magnetization saturation transfer (ST) at high field is able to reliably measure the cerebral metabolic rates of ATP involving ATPase reaction of Pi↔ATP (CMR_{ATP}) and CK reaction of ATP↔PCr (CMR_{CK})[1,2]. Moreover, it was found that the measured CMR_{ATP} reflects the net rate of oxidative phosphorylation of ADP for generating ATP in brain mitochondria and it is also sensitive to the brain activity state[3,4]. These findings indicate the great promise of *in vivo* ^{31}P ST approach for directly assessing brain ATP energy. However, the conventional ST measurement requires a fully relaxed condition before applying frequency-selected γ-ATP saturation in order to achieve accurate quantification of rate constants and fluxes. This limitation results in a lengthy repetition time (TR) and a low detection efficiency; and it poses a major hurdle for 3D CSI application in which many scans are needed. To overcome this limitation, we have recently proposed a novel strategy to improve the efficacy of steady-state ST measurement by employing a numerically optimized pre-saturation delay ($d1_{opt}$) for achieving the same magnetization transfer effect and the steady-state magnetizations of $M_{ss,Pi}$ for Pi↔ATP reaction and $M_{ss,PCr}$ for ATP↔PCr *with much short saturation time (t_{sat}) and TR* compared to the conventional ST measurements. The numerical optimization was based on solving the Block equations using known longitudinal relaxation times, estimated reaction rate constant range and a 90° excitation flip angle. The concept underlying this strategy is to seek $d1_{opt}$ for controlling the Pi and PCr magnetization recoveries to the point being near the steady-state magnetizations (i.e., $M_{ss,Pi}$ and $M_{ss,PCr}$); then, the subsequent γ-ATP saturation pulse train will further force the magnetizations to approaching the ideal $M_{ss,Pi}$ and $M_{ss,PCr}$ values which can be applied to calculate the forward rate constants (k_f) and fluxes according to the following relationships[1,2]:

$$k_{f,ATP} = (M_{c,Pi}-M_{ss,Pi})\div(T_{1,Pi}\times M_{ss,Pi}) \text{ and } CMR_{ATP}= k_{f,ATP}\times [Pi];$$

and

$$k_{f,CK} = (M_{c,PCr}-M_{ss,PCr})\div(T_{1,PCr}\times M_{ss,PCr}) \text{ and } CMR_{CK}= k_{f,CK}[PCr],$$

where T_1 presents the intrinsic longitudinal relaxation time which can be treated as constant; M_c is the magnetization acquired under fully relaxed condition in the absence of γ-ATP saturation. This new ST strategy measures $M_{ss,Pi}$ and $M_{ss,PCr}$ with a much higher efficacy, and it has been tested in the swine heart for quantifying the myocardium CK flux. In the present study, we implemented this unique ST strategy with 3D ^{31}P CSI for imaging both CMR_{ATP} and CMR_{CK} in the cat brain at 9.4T.

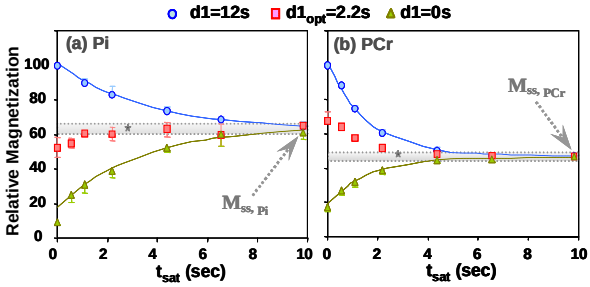

Fig. 1 Normalized signal intensity of Pi (a) and PCr (b) obtained in progressive ST experiments using varied pre-saturation delay (d1) of 12, 2.2 and 0 sec, respectively, from 1% isoflurane anesthetized cat brain (n=5) at 9.4T. The error bars represent the standard deviation and the gray zones represent the ±5% error of the steady-state signal (M_{ss}) of Pi and PCr. The ★ symbol shows typical Pi and PCr signals obtained at d1=2.2s and t_{sat}=2.8s (i.e. TR=5s) using the steady-state ST method from one representative cat brain, which are within the M_{ss} ±5% range.

METHODS All ^{1}H images and ^{31}P spectra were acquired with a home-built ^{1}H-^{31}P dual RF surface coil probe on a 9.4T/30cm bore Magnex magnet equipped with Varian INOVA consoles. Female adolescent cats under gaseous anesthesia (0.9-1.2 % isoflurane in a mixture of 70% nitrous oxide and 30% oxygen) and artificial ventilation were used for this study. The BISTRO pulse train was applied for frequency-selective saturation of γ-ATP with varied saturation time (t_{sat} up to 9.8s) for performing progressive ST measurements and a fixed t_{sat} for performing steady-state ST measurements[3]. An adiabatic half passage pulse was used for spin excitation and readout of *in vivo* ^{31}P MT spectra. The 3D ^{31}P CSI based on the 3D Fourier series window approach[4] was combined with the ST method for imaging the ATP metabolic rates. The acquisition parameters are: total scan number=112×2; FOV=4×4×2.5 cm^3; 7×7×5 phase encodes; spectra width =5000Hz; TR = 5s; and total sampling time of 18.6 minutes**.** The ^{31}P spectra were processed with LB=10 Hz before Fourier transformation and analyzed using AMARES time domain spectra fitting algorithm in the JMRUI software package. All results were presented by mean±SD.

RESULTS Figure 1 summarizes the comparison results for measuring the steady-state Pi and PCr using the progressive saturation transfer method (with varied saturation time t_{sat}) where three distinct strategies were applied. Strategy I: conventional approach with a long pre-saturation delay (d1= 12 s) for ensuring fully relaxed magnetization prior γ-ATP saturation; Strategy II: partial relaxed condition with TR << 5T_1 and without pre-saturation delay (d1=0); Strategy III: partial relaxed condition with an optimal d1 (i.e., $d1_{opt}$). The dependence of the Pi and PCr magnetizations upon t_{sat} is substantially different among the different strategies. For the first two strategies, the magnetizations change according to a mono-exponential function with a slow decay rate, thus, they require a much longer t_{sat} for reaching the steady-state magnetizations, resulting in a lengthy TR. For instance, a t_{sat} of ~10s was needed to reach $M_{ss,Pi}$, thus TR = 22 s for Strategy I and TR = 10s for Strategy II (Fig. 1a). In contrast, Strategy III uses the $d1_{opt}$ value (2.2 s) allowing the Pi magnetization recovery to the level close to $M_{ss,Pi}$, and only a short t_{sat} was required to reach $M_{ss,Pi}$ (t_{sat}: 2-3 s), thus, the same $M_{ss,Pi}$ value could be obtained with a much short TR (TR: ~5s). These optimal parameters of $d1_{opt}$ (2.2s), t_{sat} (2.8s) and TR ($d1_{opt}+t_{sat}\approx$ 5s) were applied to conduct steady-state ST measurements and the similar $M_{ss,Pi}$ and $M_{ss,PCr}$ were obtained (see * symbols in Figs. 1a and 1b). Moreover, the same parameters were used to acquire *in vivo* 3D ^{31}P ST CSI data from the cat brain. Figure 2 demonstrates the results of ^{31}P ST spectra (Figs. 2c and 2d) taken from one voxel located inside the cat visual cortex based on the brain anatomical images (Figs. 2a and 2b). It indicates that similar $M_{ss,Pi}$ and $M_{ss,PCr}$ have been reached with a short TR=5s.

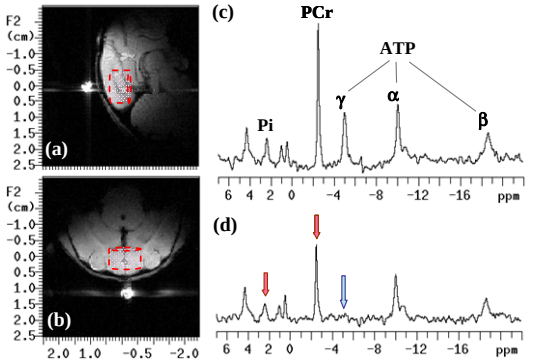

Fig. 2 Steady-state 3D-CSI ^{31}P MT measurements of cat brain at 9.4T: Anatomic images (a-b) and ^{31}P MT spectra with (d) and without (c) γ-ATP saturation obtained from a central voxel (outlined in a-b) of a representative cat brain. The 3D ^{31}P MT imaging data were acquired with d1=2.2s, t_{sat}=2.8s (i.e. TR=5s) and total acquisition time is 18.6 mins.

DISCUSSION AND CONCLUSION In this study, we examined the newly developed ST strategy combined with 3D ^{31}P CSI for measuring and quantifying CMR_{ATP} and CMR_{CK} in the cat brain at 9.4T. The main merit of this improved *in vivo* approach is to obtain the steady-state magnetizations for the chemically exchanged phosphate metabolites of Pi and PCr with substantially shortened sampling time as well as RF saturation time. It provides several advantages: i) shortening TR substantially would allow 3D-CSI acquisition within a relatively short period (e.g., Fig. 2); ii) reducing the RF saturation time or RF duty cycling rate, which is critical for minimizing the SAR concern particularly for human application; iii) increasing the sensitivity for flux measurement because short TR would allow more signal averaging within the same sampling period; and iv) significantly simplify and improve the quantification of the ATP reaction rate constants and fluxes with short TR. These advantages have been clearly demonstrated in the present *in vivo* study. The overall results indicate that the combination of the improved ST strategy and 3D *in vivo* ^{31}P CSI holds great promise for noninvasively imaging CMR_{ATP} and CMR_{CK}, which are vital for understanding the neuroenergetics and ATP energy associated with brain function and dysfunction.

References: 1. Lei et al. PNAS, 2003;100:14409. 2. Du et al. MRM, 2007;57:103. 3. Du et al. PNAS, 2008;105:6409. 4. Zhu et al. Proceeding ISMRM 2008; p 408.

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