Quantitative Measurement of Cerebral Blood Flow with High Sensitivity in Mice at 9.4T

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INTRODUCTION: Assessment of tissue perfusion in the mouse brain is challenging due to its extremely low sensitivity. Because of the there is a large database of transgenic mouse models for numerous human brain diseases, there is tremendous demand for an easy and reliable technique to ascertain CBF in mice. In this study, the combination of FAIR and single-shot kbGRASE is proposed to establish a robust protocol for quantitative measurement of CBF with high sensitivity and stability.

METHODS: Adult male C57Bl/6J mice (20~30g) were first inducted with 3% isoflurane and then maintained at 1.2% in medical air. All experiments were carried out on a 9.4T/31cm horizontal magnet (Magnex, U.K.) interfaced to a VNMRS/Direct Drive console (Varian inc., U.S.A). A 7.2-cm quadrature RF volume coil (Rapid Biomedical, Germany) was used for excitation together with a 1.2-cm single-loop surface coil for signal reception. Selective and nonselective inversions were performed by adiabatic FOCI (duration 5ms, $\beta = 2096s^{-1}$, $\mu = 4.5$) inversion pulses. CBF was quantified based on the single compartment kinetic model using the following post-labeling delay T_i values: 0.5, 0.7, 0.9, 1.1, 1.3, 1.5, 1.7, 2 and 3s. Imaging parameters were: FOV=16×16 mm^2; slice thickness=1mm; TR=5s; bandwidth= 3906 Hz/pixel; echo spacing= 120 μs. The matrix size for GRASE readout was 64×63, where 21 RF refocusing pulses and 3 gradient echoes per RF refocusing were used to generate a total of 63 echoes. A very short TE_{eff} of 4.8 ms was reached because of a dedicated kspace-banded phase-encoding ordering scheme used in kbGRASE [1]. The matrix size for EPI was 64×64 and TE 35.2 ms (full k-space single-shot EPI).

Fig. 1

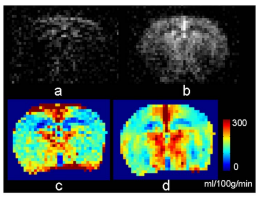


Fig. 2

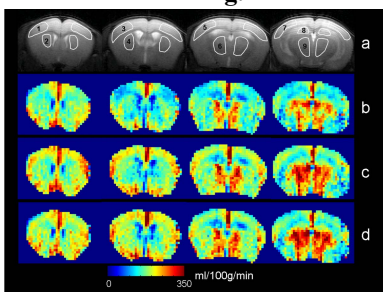
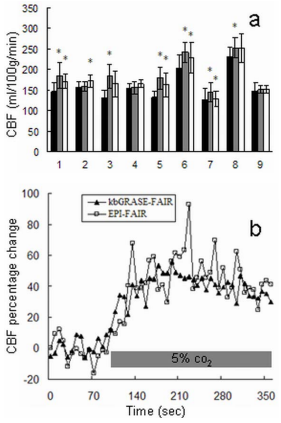


Fig. 3



RESULTS: Figs. 1a and 1b illustrate the representative difference images from a single subtraction for EPI-FAIR and kbGRASE-FAIR respectively. Image SNR and temporal SNR calculations are summarized in Table 1. The results demonstrated that group-averaged image SNR of kbGRASE-FAIR on these ROIs was 2.01±0.08 ($p<0.01$) times higher than that of EPI-FAIR and group tSNR was elevated by a factor of 2.50±0.07 ($p<0.01$). Figs. 1c and 1d show representative CBF maps from kbGRASE-FAIR and EPI-FAIR respectively. It is apparent that the perfusion map obtained using kbGRASE-FAIR gave better image quality and higher SNR.

Table 1. SNRs obtained by kbGRASE-FAIR and EPI-FAIR.

	image SNR (n=5)				tSNR (n=5)			
	LC	RC	LT	RT	LC	RC	LT	RT
GRASE	18.0±1.9	18.4±2.3	15.9±2.2	16.4±2.6	13.1±4.0	12.6±2.6	12.1±2.8	12.6±3.4
EPI	9.2±1.7	9.5±1.8	7.9±1.2	7.7±1.3	5.3±1.4	5.2±0.7	4.8±1.3	5.0±1.1
SNR ratio	1.96	1.94	2.01	2.13	2.47	2.42	2.52	2.52

LC: Left Cortex; RC: Right Cortex; LT: left Thalamus; RT: Right Thalamus.

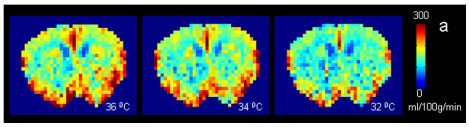


Fig. 4

Fig. 2 shows CBF quantification under different physiological conditions: (a) ROIs overlaid on anatomical T_2-weighted images; CBF maps with (b) 1.2% isoflurane with 100% air, (c) 1.2% isoflurane with premixed gas consisting of 5% CO_2 and 95% air, and (d) 1.8% isoflurane with 100% air, respectively. The corresponding CBF values (n=5, * denoted as $p<0.05$) are illustrated in Fig. 3a. Under 1.2% isoflurane mixed in 100% medical air, regional CBF values ranged between 126±27 and 231±24 ml/100g/min. The averaged CBF over 9 ROIs was 158±36 ml/100g/min. Under 5% CO_2, the averaged CBF over 9 ROIs was 184±39 ml/100g/min. Hypercapnia-induced CBF increase on the cortex regions of these 4 slices was found to be between 15% and 42%, resulting in an average of 30% ($p<0.002$) and 14% in the thalamus regions ($p<0.05$). The 1.8% isoflurane increased CBF by approximately 17~27% in the cortex ($p<0.05$) and 10% ($p<0.03$) in the thalamus, and averaged CBF across 9 ROIs was 178±38 ml/100g/min. Fig. 3b shows a representative hypercapnia-induced fMRI-like time-course based on kbGRASE-FAIR and EPI-FAIR in the cortex of a mouse. Notice the reduced instabilities in the kbGRASE time-courses. Results favored kbGRASE-FAIR in terms of measurement stability. Fig. 4 show a representative CBF map performed at core temperatures of 36°C, 34 °C and 32°C. CBF declined from 169.2 to 143.3 ml/100g/min (n=5) and 143.4 to 120.7 ml/100g/min in the cortex and caudate putamen respectively when temperature declined from 36°C to 32°C.

DISCUSSION & CONCLUSION: We demonstrated the ability of kbGRASE-FAIR to detect perfusion signal in mice with high SNR and consistent stability, without modification of existing MRI hardware. The quantitative CBF results are consistent with previously reported studies [2,3]. To study the effects of varying physiological parameters on the precision and reproducibility of CBF measurements, changes in anesthesia regime, hypercapnia and body temperature were implemented. The above results corroborate kbGRASE-FAIR as a practical and robust protocol for quantitative CBF measurement in mice at a preclinical environment of 9.4T.

REFERENCES: [1]. Feinberg DA, et al. MRM 1995; 34: 149–155. [2] Muir ER, et al. MRM 2008; 60: 744–748. [3] Kober F, et al. NMR Biomed. 2008; 21: 781–792.