Pharmacological MRI of the retina: blood flow and BOLD uncoupling during nitroprusside infusion

Y-Y. I. Shih[1], L. Guang[1], and T. Q. Duong[1]
[1]Research Imaging Institute, University of Texas Health Science Center at San Antonio, San Antonio, TX, United States

INTRODUCTION Nitric oxide (NO) is an endothelial-derived relaxing factor inducing vasodilation [1] and is an important regulator of ocular blood flow (BF) [2-4]. NO is involved in hypercapnia-induced vasodilation in the choroid and the retina. NO dysfunction has been implicated in glaucoma, diabetic retinopathy, and retinal ischemia [2,5]. Nitroprusside is a clinically used NO donor for acute hypertension treatment and vascular surgery. However, its role in regulating retinal hemodynamics is incompletely understood. In this study, we investigated the effects of nitroprusside on tissue BF and oxygenation in the rat retina using MRI. Simultaneous BF and BOLD MRI on an 11.7T scanner was made using the continuous arterial spin labeling (CASL). To our knowledge, this is the first pharmacological MRI (phMRI) application of the retina.

METHODS Six adult Long-Evans rats were anesthetized with 1.1% isoflurane and mechanically ventilated. Right femoral artery and vein were catheterized for blood pressure (BP) and blood gas measurement and subsequent drug infusion, respectively. The rat was paralyzed with pancuronium bromide (4 mg/kg first dose, 4 mg/kg/hr, i.p.) and atropine eye drop was applied topically to dilate the pupil so as to reduce motion artifact. MRI was performed on a Bruker 11.7T scanner using a small surface coil (ID~7 mm) placed on the left eye. Shimming used FASTMAP on an isotropic voxel of 7x7x7 mm, encompassing the entire eye. CASL sequence used spectral width = 192 kHz, TR = 3000 ms, TE = 13.3 ms, FOV = 9x9 mm, acquisition matrix = 90x90, yielding an in-plane resolution = 100×100 μm. Nitroprusside at different dosages (1−5 μg/kg/min, iv) was infused over 3 mins. Data were processed by linear correlation analysis, where $p<0.05$ indicates statistical significance. Nitroprusside has a diamagnetic iron (Fe^{2+}) center and phantom study confirmed no T_2* contrast even at 100 μg/ml concentration as expected.

RESULT Positive BF but strong negative BOLD response was observed in the retina, indicating a *complete BF−BOLD uncoupling* (**Fig 1**). The effects of nitroprusside on BP and BF were dose dependent. At low doses (1 or 2 μg/kg/min), nitroprusside increased BF but decreased BOLD signals (**Fig 2A**). At high dose (3−5 μg/kg/min) nitroprusside induced weak or negative BF changes and BOLD decrease (**Fig 2B**). **Fig 3** shows the BF and BOLD changes versus BP. BF and BOLD were negatively correlated with BP decreases. Blood gases showed no changes in pO_2, pH and pCO_2.

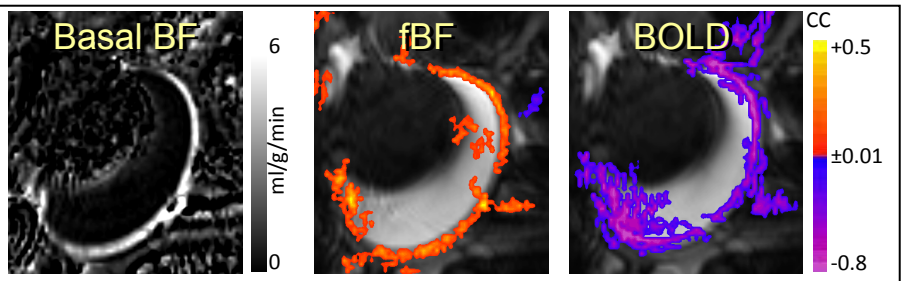

Fig 1. Basal BF and nitroprusside-induced functional BF (fBF) and BOLD changes in a rat's retina (2 μg/kg/min) where positive BF but strong negative BOLD response was observed.

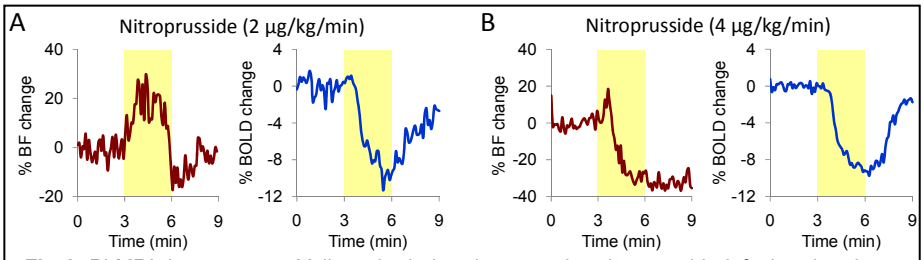

Fig 2. PhMRI time-courses. Yellow-shaded regions are the nitroprusside infusion durations. Positive BF with negative BOLD response was observed at lower infusion dosage, whereas the BF response was disrupted and turned into negative at higher infusion dose. Negative BOLD was consistently observed.

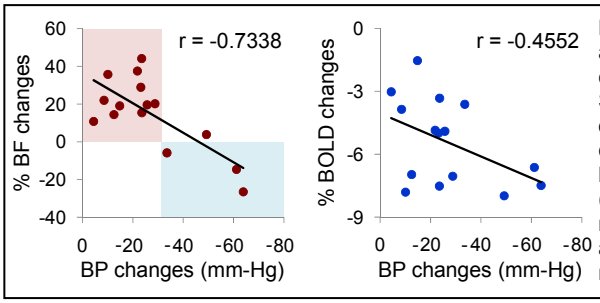

Fig 3. Nitroprusside-induced arterial BP, ocular BF and BOLD changes (n = 5, total 15 trials). Significant linear correlation was observed between BF and BP changes (p=0.0018), but not between BOLD and BP changes (p=0.0882). Positive BF responses were mainly observed at low BP changes (i.e., lower nitroprusside dosage).

DISCUSSION Nitroprusside evoked local chorioretinal vasodilation and increased ocular BF [2]. At higher dose, larger peripheral vasodilation occurred resulting in stronger BP decreases. Such peripheral vasodilation may cause "blood-steal" effect away from the retina [6] and a large decrease in BP may also disrupt vasomotor autoregulation and BF [7].

Negative BOLD response indicated decreased tissue oxygenation during nitroprusside infusion. Global O_2 concentration changes can be ruled out because no arterial blood pO_2 and pCO_2 changes were observed. The negative BOLD response with positive BF change in the retina may result from a marked increase in oxygen metabolism that exceeds the BF supply [8], resulting in decrease tissue oxygenation. Nitroprusside has been shown to produce hypotension in dogs with brain tissue oxygen pressure decreased 50%, but not with 3% isoflurane-induced hypotension [9]. In addition, negative BOLD response has also been reported in many brain regions after nitroprusside injection [10]. Together, these suggest that nitroprusside markedly alters oxygen tension in the retina.

CONCLUSION This study demonstrates fMRI of a pharmacological challenge in the retina. These findings may have strong implications for neurovascular coupling mechanism and suggests caution to be exercised when using nitroprusside for patients with retinal diseases. Future studies will improve spatial resolution to visualize potential differential responses in the retinal and choroid circulations, and employ pO_2 electrode to confirm tissue oxygenation changes in the retina during nitroprusside infusion.

REFERENCE [1] Palmer et al., *Nature* 1987, 327:524. [2] Schmetterer et al, *Prog Retin Eye Res* 2001, 20:823. [3] Mann *IOVS* 1995,36:925. [4] Huemer et al, *Invest Ophthalmol Vis Sci* 2007, 48:4215. [5] Berkowitz et al., *Diabetes* 2004, 53:173. [6] Harel et al., *JCBFM* 2002, 22:908. [7] Severinghaus et al., *J Appl Physiol* 1958, 12:485. [8] Schridde et al., *Cereb Cortex* 2008, 18:1814. [9] Hoffman et al., *Anesth Analg* 2001, 93:166. [10] Henderson et al., *J Appl Physiol* 2004, 96:693.