Blood-Flow Magnetic Resonance Imaging of the Retina

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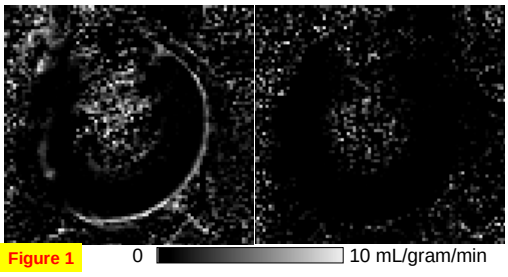
INTRODUCTION Blood flow (BF) in the retina is tightly regulated and intricately coupled to basal metabolic function under normal physiological conditions. Perturbations of basal BF and its coupling to metabolic function have been implicated in many retinal diseases. While basal BF, stimulus-evoked and pathology-induced BF changes have been well described in the brain, BF MRI in the retina has not been demonstrated because very high spatial resolution and sensitivity are needed to visualize the thin retina. This study explored the feasibility of imaging basal BF, physiologically induced, isoflurane-induced BF changes in the rat retina using MRI. This approach extends our recent reports on structure (1,2) and functional (BOLD) MRI of the retina (2,3) and has the potential to complement existing retinal imaging techniques.

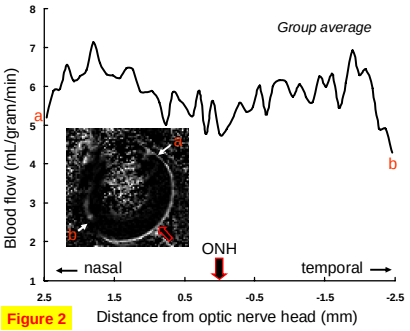
Methods Six male rats (350-400g) were imaged under ~1% isoflurane, paralyzed and mechanically ventilated. End-tidal CO_2, heart rate and O_2 saturation and rectal temperature were maintained within normal physiological ranges unless purposefully altered. BF was measured at 7T (Bruker) using the arterial spin-labeling technique with a separate neck labeling coil, a small eye coil, four-shot EPI with a FOV=11.5x11.5mm, matrix 128x128 (90x90 µm), slice thickness=1.5mm, TR=3s per shot, and TE=14ms. Each trial was 6 mins air and 6 mins of 100% O_2 or 5% CO_2 in air. BF images were calculated as described elsewhere (4). To avoid bias, automated profile analysis (2) was performed. BF profiles were plotted across the thickness of the retina and along the length of the retina.

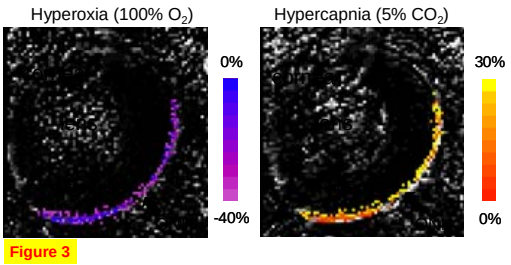
RESULTS **Figure 1** shows the BF retinal image in a live and postmortem animal (same animal). Among ocular structures, BF was greatest in the retina. *Post-mortem* animals showed no statistically significant BF contrast in the retina. **Figure 2** shows the group-average blood flow as a function of distance from the optic nerve head (ONH). Blood flow is relatively constant across the length of the retina, except it dipped slightly at the optic nerve head and dropped significantly at the distal edges where the retina terminates. **Figure 3** shows the BF %-change maps associated with physiologic challenges. Hyperoxia decreased BF whereas hypercapnia increased BF as expected. **Figure 4** shows the BF profiles across the retinal thickness before and during physiologic challenges. BF values during air, 100% O2, and 5% CO2 breathing were 6.3±1.0, 4.8±0.6, and 7.3±1.1mL/gram/min (P<0.05 *versus* air). Moreover, BF increased to 9.3±2.7mL/gram/min under 1.5% isoflurane in air (P=0.006).

DISCUSSION Basal BF of the retina is significantly higher than cerebral BF (~1mL/g/min (4)) under essentially identical experimental conditions, and this finding is consistent with that report using the microsphere technique (5). We observed hyperoxia-induced vasoconstriction, consistent with those that reported BF decrease by 30% using Heidelberg Flowmeter (6) and 60% using laser Doppler flowmetry (7). In the brain, oxygen inhalation in awake humans elicits only 13% CBF reduction (8). While there are some evidence that hypercapnia elicits vasodilation in both *retinal* and *choroid* blood vessels using LDF and microsphere techniques, the literatures are sparse and controversial (9-10). Our results indicate that there is consistent and significant BF increase with 5% CO_2 inhalation. In the rat brain, 5% CO2 inhalation increased cerebral BF by 25%-52% (4). The smaller change in the retina may be due to the high basal *choroidal* BF. The use of isoflurane could further accentuate this effect. Indeed, BF in the retina increased 48% when isoflurane is increased from 1 to 1.5%, consistent with isoflurane being a vasodilator and its effects on CBF (4). Together, these results indicate that blood-flow regulation is unique in the retina. Given the spatial resolution, the BF and BF changes reported at current spatial resolution are a weighted average BF of the two vascular layers in the retina bounding the retina, namely the *retinal* and *choroidal* vascular layers. Improving spatial resolution to distinguish BF and BF changes in the two vascular layers is likely important and is under investigation.

CONCLUSION This study demonstrates a proof of principle that quantitative BF in the thin retina and its responses to physiologic stimuli can be reliably imaged using MRI with large field of view and without depth limitation. Future studies will focus on improving resolution to detect lamina-specific BF and visually evoked BF responses. MRI has the potential to provide unique information on how BF *at the tissue level* (as opposed to large vessels) is regulated and how retinal diseases may affect BF and the neural tissues they subserve. Blood-flow MRI has the potential to provide unique insights into retinal physiology and could serve as an early biomarker for retinal diseases.







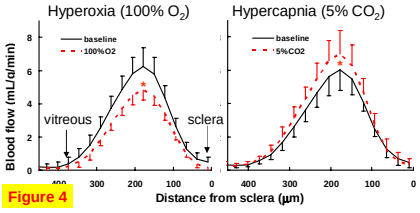


Fig 1. Retinal BF image of in live (left) and postmortem (right) animal. **Fig. 2.** BF values across the length of the retina. **Fig 3.** BF % change maps associated with hyperoxia and hypercapnia. **Fig 4.** BF profiles across the retinal thickness under baseline, 5%CO_2 and 100%O_2 from group-average data. * P<0.05.

References. 1) Shen et al. JMRI 2006, 23:465. 2) Cheng et al., PNAS 2006, 103:17525. 3) Duong et al., IOVS 43:1176. 4) Sicard & Duong 2005, 25:850. 5) Alm & Bill Exp Eye Res 1973, 15:15. 6) Sternn et al., Br J Ophthal, 1997, 81:360. 7) Strokel, Arch Ophthal, 1965, 73:838. 8) Kety & Schmidt, J Clin Invest, 1948, 27:484. 9) Geiser et al., Curr Eey Res 2000, 21:669. 10) Frayser and Hickam, IOVS 1964, 3: 427