Layer-Specific Retinal and Choroidal Blood-Flow MRI in a Mouse Model of Glaucoma

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INTRODUCTION: Glaucoma, a leading cause of irreversible blindness worldwide, is characterized by a progressive degeneration of retinal ganglion cells and the optic nerve. Glaucoma is often associated with elevated intraocular pressure (IOP). A longstanding hypothesis is that elevated IOP compresses ocular blood vessels, reducing blood flow (BF) in the eye. The retina is nourished by two separate vasculatures: the retinal vessels located in the inner retina next to the vitreous and the choroidal vessels behind the retinal pigment epithelium. The retinal layers composed of the photoreceptor cells between the two vascular layers are avascular (1). MRI has recently been used to quantify RBF and ChBF in mice at 42x42x400 μm (2). MRI was used to test the hypothesis that layer-specific RBF and ChBF are reduced in a mouse model of glaucoma with elevated IOP.

METHODS: The DBA/2J mouse model of glaucoma develops an optic neuropathy similar to glaucoma. Age-matched normal C57BL/6 mice were used for controls. MRI was done on mice at 4, 6, and 9 months of age (n= 40 total). Mice were imaged under 1.2-1.6% isoflurane in 30% oxygen and spontaneous breathing. Respiration rate, heart rate, oxygen saturation and temperature were maintained within normal ranges. MRI was performed on a 7T/30cm Bruker scanner with a 150 G/cm gradient and a small surface eye coil with active decoupling (diameter=6mm) and a circular coil (diameter=8mm) for arterial spin labeling placed at the heart (2). Images were acquired in coronal orientation with gradient-echo EPI with FOV=6x6 mm, matrix=144x144 zero-filled to 256x256, 2 segments, a single 0.4 mm slice, TR=3.0s per segment, TE=9.7ms, labeling duration=2.9s, and post labeling delay=10ms. BF images in ml/g/min were calculated as in (2). Profile analysis was used to average BF along the retinal length (1). Statistical analysis used two-way ANOVA with Bonferroni post-hoc tests.

RESULTS: BF images from C57BL/6 and DBA/2J mice had two BF layers corresponding to RBF and ChBF, which were separated by a region of low BF corresponding to the avascular region (**Figure 1**). **Figure 2** summarizes RBF and ChBF from C57BL/6 and DBA/2J mice at all ages. ChBF was significantly reduced in DBA/2J mice at all ages compared to age-matched C57BL/6 mice, while RBF trended lower but was significantly reduced only at 9 months.

DISCUSSION: Increased IOP, a risk factor for primary open-angle glaucoma (POAG), occurs in DBA/2J mice by 6 months of age along with optic neuropathy consistent with human POAG (3,4). These DBA/2J mice have significant axonal loss in the optic nerve over time. Increased IOP may compress retinal and choroidal vessels and impede ocular BF. Decreased ocular blood flow may result in ischemia and contribute to retinal damage in glaucoma. Both RBF and ChBF were decreased in aged DBA/2J mice, consistent with the hypothesis that the glaucoma-like optic neuropathy of DBA/2J mice is caused by dysregulated ocular BF. The ChBF deficit preceded the RBF deficit and may elicit ischemic hypoxia in the photoreceptors. If BF is chronically reduced at the prelaminar and laminar optic nerve, axon damage may occur due to tissue hypoxia or reactive oxygen species (3,4).

We show that the DBA/2J mouse model of glaucoma has layer-specific reductions of RBF and ChBF. This finding is consistent with the hypothesis that ischemia is involved in glaucoma. Future studies will investigate functional BF responses to physiological stimulations during disease progression. ASL MRI has the potential to offer depth-resolved, quantitative BF data that may prove useful for glaucoma disease staging and monitoring of therapeutic treatments.

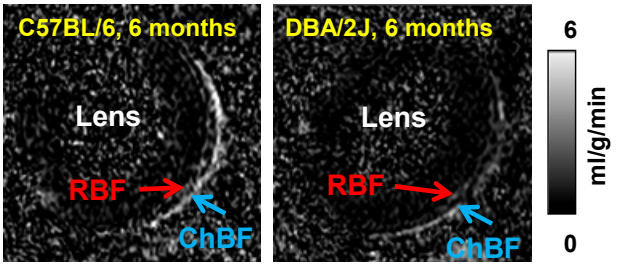

Figure 1. Quantitative BF maps of C57BL/6 and DBA/2J mouse eyes at 6 months of age at 42x42x400 μm.

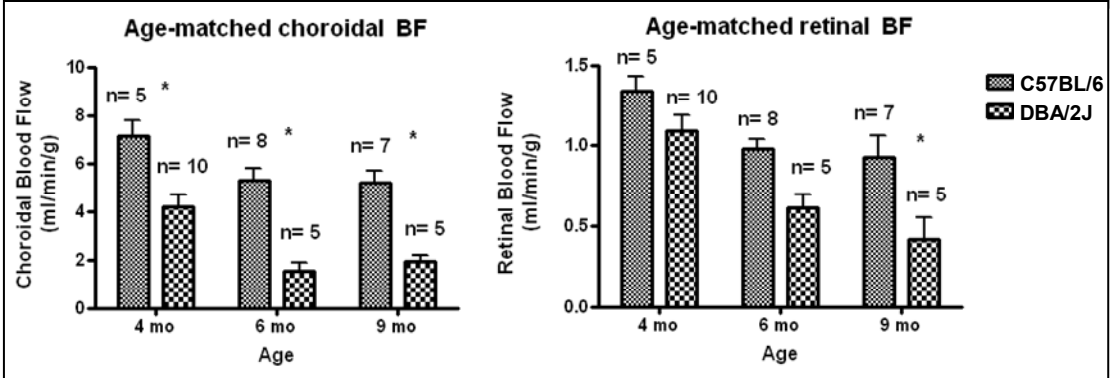

Figure 2. Group-averaged ChBF and RBF in C57BL/6 and DBA/2J mice at 4, 6, and 9 months of age (mean±SEM). *p<0.05.

Reference: 1) Cheng et al, PNAS 2006, 103:17525. 2) Muir et al, NMR Biomed 2010, in press. 3) Kwon et al, NE J Med 2009, 360:1113. 4) Inman et al, IOVS 2006, 47:986. Supported in part by R01 EY014211, R01 EY018855, VA MERIT, and a UTHSCSA URC award.