Layer-Specific Blood-Flow MRI of Retina Degeneration at 11.7T

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Background: Retinitis pigmentosa (RP) is a family of retinal diseases. The Royal College of Surgeons (RCS) rat (1) is an established animal model of RP with a mutation in the Mertk gene. This mutation leads to impaired phagocytosis of the photoreceptor segments by the retinal pigment epithelium, resulting in spontaneous photoreceptor degeneration similar to human patients with RP. Many novel treatments are currently being tested.

Blood flow (BF) to the retina is supplied by two separate circulations, the retinal and choroidal vasculatures. Retinal blood flow (RBF) and choroidal blood flow (ChBF) may be altered in retinal diseases including RP. Thus the ability to image laminar specific blood flow (BF) could have important applications for staging diseases and testing novel therapeutic interventions. While the retina is commonly studied using optical techniques, MRI has the unique advantage of providing depth-resolved anatomical, physiological and functional data. Advances in MRI technologies have allowed very high spatial resolution capable of laminar resolution in the thin retina. BF MRI of the retina has been reported in normal and RCS rat retinas but without laminar resolution (2). This study explored high-resolution, layer-specific BF MRI to image quantitative RBF and ChBF in normal and RCS rat retinas at 11.7T with 43x43x600 μm resolution. High field was utilized to gain SNR and BF contrast.

Method: RCS rats (n = 5 at postnatal day 90~120) and age-matched normal control rats (n = 6, about postnatal day 90~110) were paralyzed with pancuronium, ventilated and anesthetized under ~1% isoflurane. ETCO2, O2 saturation, heart rate and rectal temperature were monitored and maintained within normal ranges. MRI was performed on a 11.7 T/16 cm Bruker scanner with a 77 G/cm gradient and a small surface eye coil with active decoupling (ID=1 cm) and a butterfly neck coil for arterial spin labeling placed at the neck. BF MRI of a single axial slice bisecting the optic nerve was acquired using arterial-spin labeling technique and gradient-echo inversion-recovery EPI with 10x10 mm FOV, 2.0 s labeling pulse, 4.0s TR per segment, 2.1s TI (which occured during labeling duration), 228x228 matrix zero-padded to 256x256, single 0.6 mm slice, 6 segments, and 15.4 ms TE. Typically, 20 pairs (labeled and non-labeled) of images were acquired for averaging. BF profiles across the retinal thickness were obtained (2).

Results: Figure 1A shows a representative BF image of a normal retina. RBF and ChBF layers and the avascular layer in between are well resolved. Figure 1B shows the group-averaged BF profiles across the retinal thickness. BF profiles of the normal retinas (n=6) showed two well-resolved peaks corresponding to retinal and choroidal vascular layers, while the BF profiles of the RCS retinas showed only one peak (4 rats hadone peak, 1 had a very small retinal peak).

In normal rats, the RBF was 0.93±0.41 ml/g/min and ChBF was 7.4±1.48 ml/g/min. In RCS rats, only a single BF peak remained with a value of 7.3±2.1 ml/g/min. BF of the single peak in RCS rats was not significantly different ($p = 0.9$) from ChBF of normal controls. However, the RBF in the normal control is 80% higher ($p = 0.02$) than that in RCS rats.

Histological thickness confirmed atrophy of the outer nuclear layer and the photoreceptor segments (Figure 2). In this animal, atrophy was also detected in the inner nuclear layer. The total thickness, excluding the choroid, was 191±3 μm for controls and 105±18 μm for RCS rat retinas.

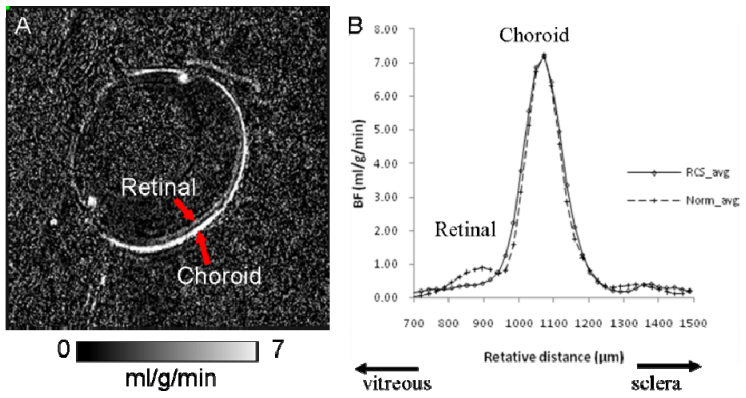

Figure 1. (A) BF MRI of the retina at 43x43x600 μm from a single animal. (B) Group-averaged BF profiles across the retinal thickness for normal and RCS rat retinas.

Discussion & Conclusion: This study demonstrated for the first time, very high resolution, layer-specific BF in the rat retina at 11.7T. In normal retinas, ChBF was 8x higher than RBF, consistent with microsphere studies (4). Moreover, in RCS retinas at about P100, where histology showed essentially complete degeneration of the outer nuclear layer and the photoreceptor segments, only one BF peak was detected. A possible explanation is that the retinal vasculature had deteriorated. This interpretation is supported by 1) Nilsson et al (6) who reported RBF severely decreased but ChBF is not significantly affected in a cat model of retinal degeneration using microspheres. 2) Vascular damage in retinal circulation of RCS rat retinas was detected despite the inner retina appearing relatively intact in histology (5). An alternative explanation is that the single BF peak in the RCS rat retina was a result a merging of retinal and choroid peaks from the loss of the avascular layers in between. Indeed, the single BF peak in the RCS retina was slightly wider than the ChBF peak in normal retinas. We believe that both situations (deterioration of RBF and loss of the avascular layer) likely occurred. Moreover, another previous report found that MRI BF of the total retina (without laminar resolution) decreased significantly in RCS rats compared to controls (2). These apparent discrepancy remains to be investigated. However, caution must be exercised, when comparing data across laboratories because, not only did BF measurement techniques differ, but RCS rats might have been at different stages of retinal degeneration).

In conclusion, MRI is the only in vivo blood-flow imaging method that is capable of imaging RBF and ChBF. BF is perturbed associated with retinal degeneration. High resolution, layer-specific BF MRI may prove useful for studying retinal diseases, monitor disease progression and test novel therapeutic interventions in animal models.

References 1) Gal et al, Nat Genet 2000 , 26:270. 2) Li et al. IOVS 2009, 50:1824. 3) Cheng et al., PNAS 2006, 103:17525. 4) Alm & Bill, Exp Eye Res 1973, 15:15. 5) Wang et al, Curr Eye Res 2003, 27:183. 6) Nilsson et al., IOVS 2001 42:1038.

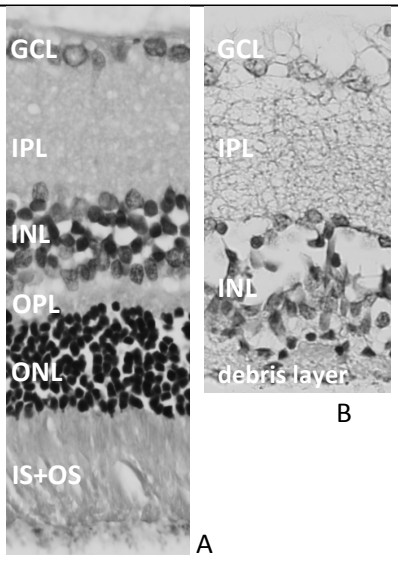

Figure 2. Histology of a normal (A) and a RCS retina (B). Ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), and inner and outer segments (IS+OS).