

The effects of Dorzolamide on retinal and choroidal blood flow in a mouse glaucoma model

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TARGET AUDIENCE: Researchers interested in glaucoma, eye disorders, arterial spin labeling, cerebral blood flow etc.

PURPOSE: Dorzolamide (DZ) is a carbonic anhydrase inhibitor, which is used to reduce aqueous humor production, and thus intraocular pressure (IOP) ^{1,2}. DZ is clinically used to treat glaucoma. However, the effects of DZ on retinal blood flow (RBF) and choroidal blood flow (ChBF) are unknown. The goal of this study is to investigate the effect of topical DZ application on RBF and ChBF in DBA/2J mice, an established mouse model of glaucoma. Results are compared with C57BL/6J mice, used as a control group.

METHODS: Male wild-type (WT) C57BL/6J mice aged 4 months (n=8), and male DBA/2J mice aged 4 months (n=7) and 9 months (n=6) were used for this *in vivo* MRI study. The mice were anesthetized with 1-1.2% isoflurane. Temperature was maintained at 37°C and respiratory rate at 80-110 bpm. MRI scans were performed in a 7T magnet (Bruker Biospec) with a 150 Gauss/cm gradient using a custom eye coil for imaging (ID=0.6 cm) and a heart coil for ASL (ID=0.8 cm) as described previously [3]. The BF scans were acquired with a GE-EPI sequence with FOV=0.6x0.6cm, matrix=144x144 zero-filled interpolation to 256x256, 400 µm coronal slice, 2 shots, labeling duration=2.94s, TR=3s, and TE=9.8ms. Once the initial scans were acquired (before treatment), a single drop (5 µl) of Dorzolamide HCl Ophthalmic Solution, 2% (Bausch+Lomb) was applied on the eye. MRI was acquired 1 and 2 hrs after DZ application.

RESULTS: **Figure 1A** shows a layer-specific blood flow image from a WT mouse eye. Scale bar indicates blood flow values from 0 to 6 mL/min/g. **Figure 1B** illustrates RBF and ChBF profiles.

Figure 2 plots the ChBF and RBF before and after DZ application. ChBF (blue bars) were lower in the 4-mo DBA/2J mice than in the 4-mo WT, but did not reach statistical significance. Basal ChBF in the 9-mo DBA/2J mice was statistically lower compared to WT (p<0.01) and 4-mo DBA/2J (p<0.05).

At 1-hour post DZ, ChBF increased in all animal groups, although significance was achieved only in the 9-mo DBA/2J ChBF, and in the 4-mo WT RBF. At 2 hrs post DZ, choroidal BF generally dropped slightly below pre-DZ levels, except choroid BF at 9 months DBA/2J which remained elevated.

The RBF followed similar patterns with a few exceptions, namely that, at 2 hrs post DZ, retinal BF at 4 and 9 mo remained elevated.

DISCUSSION: The DBA/2J mouse develops increasing IOP with age. This is expected to reduce perfusion pressure, and thus ChBF and RBF, in a progressive manner. We indeed observed significant and progressive reductions in basal ChBF and RBF with glaucoma severity. Our finding is consistent with a previous study.³

At 1-hr post DZ, ChBF and RBF increased significantly or trended higher in all animal groups, suggesting DZ exerts the expected acute effects of reducing perfusion pressure and IOP. In general, this effect is transient lasting about an hour after DZ application in the WT and early stage of glaucoma (4 months). This effect appears more sustained lasting at least to 2 hrs after DZ application in the later stage of glaucoma (9 months).

CONCLUSIONS: DZ induces transient increase in ChBF and RBF in WT and early stage of glaucoma, but induces a more sustained effect in the later stage glaucoma. Future studies will investigate the effects of chronic DZ treatment on ChBF and RBF in DBA/2J mice. Blood flow MRI has the potential to provide a complementary and objective physiological parameter for evaluating novel interventions and dosing regimens in glaucoma.

REFERENCES: [1] Casson, Clin Exp Oph 2012;40:341. [2] Fuchsäger-Mayrl, Br J Ophthalmol. 2005, 89:1293. [3] Lavery, IOVS 2012;53:560.

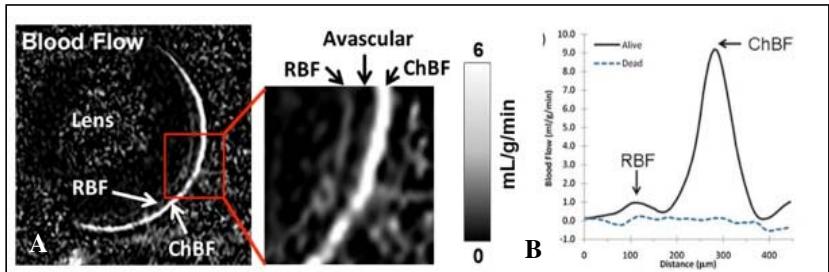


Fig 1: (A) Layer-specific blood flow image from a WT mouse eye. Scale bar indicates blood flow values from 0 to 6 mL/g/min. (B) Retinal BF and choroidal BF profiles from (A)

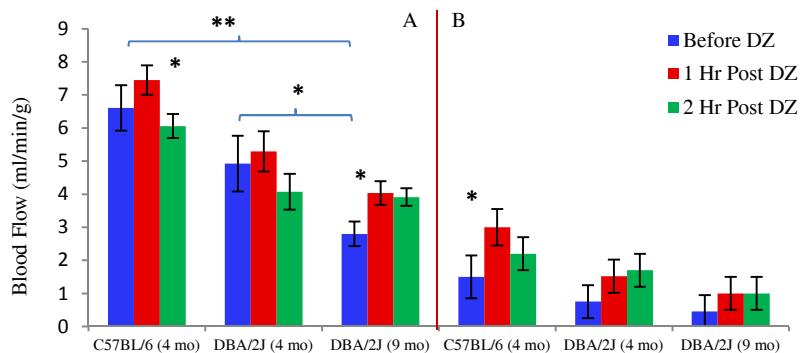


Fig 2: Effects of DZ administration (up to 2 hours post DZ) on (A) the choroid blood flow and (B) retinal blood flow. SEM, * p<0.05, ** p<0.01