Magnetic Resonance Imaging of Blood Flow of the Human Retina

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INTRODUCTION Blood flow (BF) is intricately coupled to basal metabolic function under normal physiological conditions, and it is often perturbed in disease states (1), such as glaucoma, diabetic retinopathy, and retinal ischemia. In vivo BF imaging of the retina has been reported using optical techniques such as fluorescein angiography, indocyanin-green angiography, laser Doppler flowmetry and laser speckle imaging. These methods are generally qualitative and depth ambiguous. Moreover, optical scattering and disease-induced opacity, such as vitreal hemorrhage and cataract, could hamper efficacy of optical imaging techniques.

The goals of the present study were to explore the feasibility of imaging BF and BF responses of hypercapnic (5% CO_2, 21% O_2 and balanced N_2) inhalation in the unanesthetized human retina using MRI. Pseudo-continuous arterial spin-labeling technique (pCASL) (2) with background suppression and single-shot turbo spin-echo (TSE) acquisition was implemented. pCASL was used to improve BF sensitivity, background suppression was used to enhance sensitivity and minimize eye movement artifacts, and TSE was used to achieve high spatial resolution free of susceptibility-induced signal drop off. Quantitative basal BF and hypercapnia-induced BF changes were analyzed.

METHODS Experiments were performed on 5 normal human volunteers with 2 or 3 repeated measurements made on each subject. Subjects were asked to blink if needed right after the data readout train but otherwise fixated on a point during MRI. For gas challenge, serial BF MRI was acquired during 4 mins air followed by 4 mins hypercapnia. Premixed gas was delivered *via* an inhalation face mask. The total scan duration for each trial was 8 mins.

MRI studies were performed on a 3T Philips Achieva with an oval (7x5cm) single-loop RF coil. BF was imaged using the pCASL technique with labeling duration=2s and post-labeling delay=1.5s. The ASL labeling plane was 7 cm inferior to the imaging plane. ASL background suppression employed two inversion pulses at 2061 and 3405 ms after the initial saturation pulse, which was placed before the labeling (3). Image acquisition utilized the single-shot TSE sequence with: TR/TE=4.6s/30ms, slice thickness=6mm, bandwidth=12.8kHz, TSE factor=28, FOV=50x43mm, and matrix=100x53 (resolution of 500x800μm). Basal BF measurements during air inhalation were acquired over 8mins. A reference scan with TR=15s was used to derive M_0 for BF quantification. Basal BF was analyzed along the length of the retina and across the retinal thickness. Activation maps responding to hypercapnia were analyzed using standard FSL FEAT package (FMRIB Software Library, FMRIB, Oxford, UK).

RESULTS **Figure A** shows a scout image demonstrating the anatomical structure of the eye. Quantitative BF image showed excellent BF contrast under basal condition, with high BF localized to the posterior retina (**Figure B)**. BF in the retina was markedly above noise level as indicated by the negligible BF values in the vitreous and sclera. The BF profile was analyzed as a function of distance from optic nerve head (**Figure C**). BF showed a strong spatially dependent distribution. It peaked around the fovea regions, dipped slightly around the optic nerve head relative to its surrounding, and dropped significantly at the distal edges of the retina.

Hypercapnic inhalation increased BF and the response was localized to the posterior retina (**Figure D**). The BF profiles under air and hypercapnia are shown in **Figure E**. The group-averaged BF in the ROI at the posterior retina was 93±31mL/100mL/min (mean±SD, N=5). Hypercapnic inhalation increased BF by 12±2% relative to air inhalation (P<0.01, paired t-test).

DISCUSSION This study demonstrates a proof of concept that *quantitative* basal BF and its responses to hypercapnic challenge in unanesthetized human retina can be imaged using non-invasive MRI. Basal BF of the total retina, including the choroid was 93±31 mL/100mL/min in unanesthetized humans. To our knowledge, there is no previously reported quantitative BF in the in vivo human retina with which to compare. In animal model, basal BF of the rat retina has been reported to be 630 ± 100 mL/gram/min under 1% isoflurane using continuous ASL MRI (4). The differences in BF of the retina between humans and rats could arise from species differences, spatial resolution differences, and the effect of isoflurane (a vasodilator) in rats.

CO_2 has a strong vasodilation effect. Retinal BF increases dramatically during hypercapnia inhalation (5), while choroidal BF has been reported to increase or remain constant (5,6). Although our current resolution of BF MRI cannot resolve two vascular layers, hypercapnia inducing BF increase in the retina/choroid complex is consistent with the literature. In isoflurane-anesthetized rats, hypercapnic inhalation increased BF by 16 ± 6 % using BF MRI (4). BF MRI of animal and human retinas show consistent positive BF increases during hypercapnic inhalation.

CONCLUSION With improvement in spatiotemporal resolution and sensitivity, MRI has the potential to provide unique, clinically relevant, depth-resolved information on how BF is regulated and how retinal disease affect BF, as well as to serve as a biomarker for staging disease, and testing novel therapeutic strategies. Similarly, BOLD fMRI of the in vivo human retina has also recently been reported (7). The MRI approach could open up new avenues for retinal research and complement existing retinal imaging techniques.

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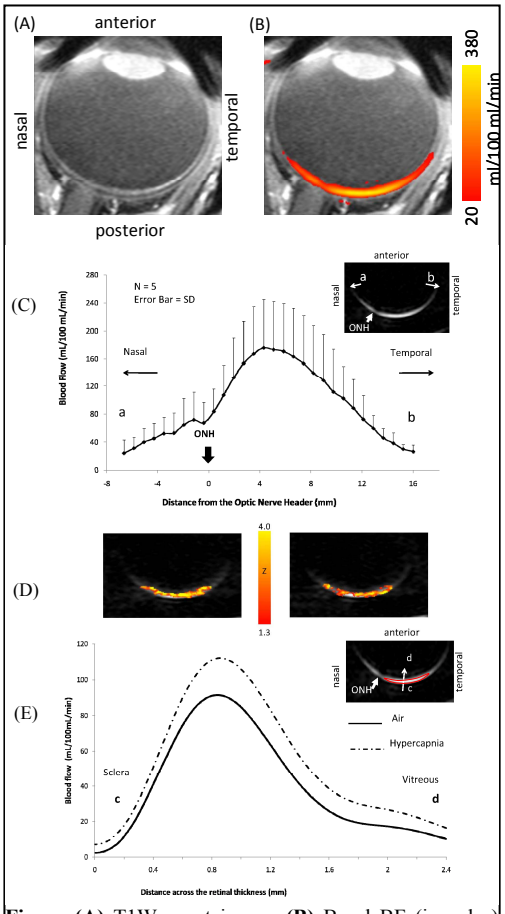

Figure (A) T1W scout image. **(B)** Basal BF (in color) overlaid on a scout image. **(C)** Averaged basal BF as a function of distance from the optic nerve head (ONH). **(D)** Activation maps from two repeated trials from the same subject. Color maps are overlaid on the BF images. **(E)** BF profiles under air (solid line) and hypercapnic inhalation (dotted line) across the retinal thickness. Profile was obtained from the posterior retina ROI.