

BLOOD FLOW MRI OF THE HUMAN RETINA DURING ISOMETRIC EXERCISE-INDUCED INCREASE IN BLOOD PRESSURE

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INTRODUCTION Improved understanding of the relationship between perfusion pressure and blood flow (BF) in the retina is important because of its relevance to the understanding of BF autoregulation and pathophysiology [1]. While optical imaging techniques have been used to investigate BF after exercise, similar studies during exercise are limited due to eye movement [2-3]. Isometric exercise (such as handgrip) in which resistance involves muscle contraction in a static position (in contrast to dynamic exercise) can acutely increase mean arterial pressure (MAP). This is done non-invasively without pharmacologic manipulation, avoiding potential drug side effects. Moreover, it can be used in a MRI environment.

This study utilized an innovative MRI application to investigate quantitative basal BF and BF changes in the retina/choroid complex associated with isometric exercise in humans. Physiological measurements included MAP from the contralateral arm, intraocular pressure (IOP), heart rate (HR), respiratory rate (RR), end-tidal CO₂ (EtCO₂) and arterial oxygen saturation (SaO₂).

METHODS Experiments were performed on 4 healthy subjects with normal vision with 2 or 3 repeated measurements made on each subject. BF MRI data of the retina was measured continuously during which subjects rested for 1 minute (min), then squeezed a tennis ball for equal duration. The rest-exercise cycle was repeated 3 times, followed by 1 min of rest. Subjects were instructed to maintain stable fixation on a target inside the magnet bore and blink only at the end of data readout which generated a distinct sound as a cue. MAP from the contralateral arm was measured during fMRI scans. IOP, HR, RR, EtCO₂ and SaO₂ were measured on the same subjects under identical experimental conditions but outside the MRI scanner. Ocular perfusion pressure (OPP) was calculated as MAP-IOP [4].

BF MRI was performed on a 3.0 T Philips Achieva System using a custom-fit receive-only surface coil (~7 cm in diameter). High resolution BF MRI (0.5x0.8x3 mm³) was acquired on a single central axial slice bisecting the optic nerve head and fovea using the pseudo-continuous ASL technique with background suppression and single-shot turbo-spin echo (TSE). SAR was well below the FDA maximum recommended limit. All measured parameters were analyzed for resting and isometric exercise states. All statistical tests employed a one-way ANOVA with correction for correlated samples with $P < 0.05$ indicating statistical significance.

RESULTS: Figure 1 shows basal BF MRI, BF activation map, and response time course associated with isometric exercise. Basal BF in the posterior retina was 137 ± 47 mL/100mL/min (\pm SD, N=4 subjects) with a mean heart rate of 59 ± 4 bpm, mean arterial pressure of 77 ± 7 mmHg, and ocular perfusion pressure of 66 ± 5 mmHg. Isometric exercise significantly increased mean BF by $44 \pm 15\%$, HR by $21 \pm 8\%$, MAP by $20 \pm 8\%$, and OPP by $27 \pm 6\%$ for all but did not change IOP, SaO₂, EtCO₂, and RR ($P > 0.1$ for all) (Figure 2).

DISCUSSION Isometric exercise robustly increases BF in the retina. Because choroid BF is 4-10 times higher than retinal BF [5], these changes likely reflect predominant choroidal BF changes. Our isometric exercise paradigm is considered very mild compared to leg extension (moderate) and squatting (strong) [2]. Moreover, handgrip was applied unilaterally. Thus, we were surprised by the marked increases in MAP and BF. BF increase during isometric exercise could be a result of increased EtCO₂, passive increased OPP, and autonomic system activities.

EtCO₂ could increase due to involuntarily breath-hold during isometric exercise and could thus contribute to BF increase [6]. However, no significant EtCO₂ and RR changes were detected in our study, which enable us to rule out this possibility.

OPP increase (30%) could directly increase BF (44%). This is contradictory to a previous study which found no significant changes in retinal BF during isometric exercise until OPP exceeded the rest value by 40% using laser Doppler velocimetry [2]. Another study using laser Doppler flowmetry reported that choroidal BF is autoregulated by vascular resistance in proportion to increase in OPP up to ~67% above resting levels, capable of maintaining choroid BF within 10% of baseline [3]. The discrepancy between this and previous studies could be due to difference in methodologies. Subjects were in an up-right position in previous studies, but in a supine position in the current study. This disparity could cause OPP differences. In addition, optical techniques are depth ambiguous and limited to macular or optic nerve head. Optic nerve head contains large arteries and draining veins which generally vasoreact less than smaller vessels. BF MRI measures changes in smaller vessels.

A likely explanation of marked MAP and BF increases is a result of autonomous system control. The retina/choroid complex is innervated by sympathetic and parasympathetic pathways [7] and sympathetic activation could cause large vessel constriction and small vessel dilation in brain [8]. Irrespective of the cause of MAP changes, this study establishes BF MRI of the retina and a simple isometric exercise paradigm to study the relation of perfusion pressure and BF in the retina of unanesthetized humans in a non-invasive MRI environment.

CONCLUSION This study demonstrates quantitative BF MRI during rest and isometric exercise in the retina of unanesthetized human using MRI. Ocular BF increase was observed in mild isometric exercise. BF MRI of isometric exercise can be used to investigate autoregulatory dysfunction in patients with retinal diseases non-invasively without pharmacologic manipulation. Future studies will need to improve sensitivity and spatiotemporal resolution to separately measure retinal and choroid BF, as well as incorporate 3D BF and other MRI (i.e., BOLD) methods.

REFERENCES [1] Risner, D., et al. *J. Glaucoma* 18(6): 429, 2009. [2] Robinson, F. et al, *IOVS* 27(5): 722, 1986. [3] Riva, C.E. et al, *IOVS* 38(11): 2338, 1997. [4] Lovasik, J., et al. *Optom Vis Sci* 70(12): 1005, 1995. [5] A. Bill, *Handbook of physiology Part 2, Microcirculation*, Renkin, Michel, Eds. 1984. [6] Schmetterer, L. et al. *IOVS* 39(7): 1210, 1998. [7] Alm, A. *Exp Eye Res* 25(1): 19, 1977. [8] Harper, A., *Arch Neurol* 27(1): 1. 1972.

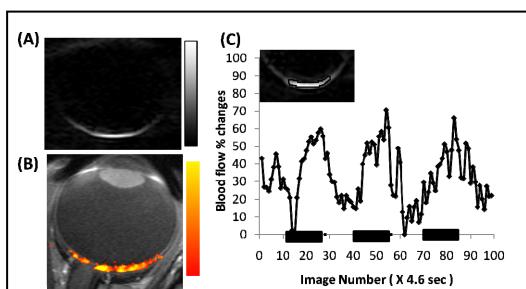


Figure 1. (A) Quantitative BF during rest, (B) activation map and (C) time course time during rest and isometric exercise (3 black rectangular blocks) from one trial from one subject. Grayscale bar: 0-380 ml/100ml/min. Color bar: Z score 2.3-6.0

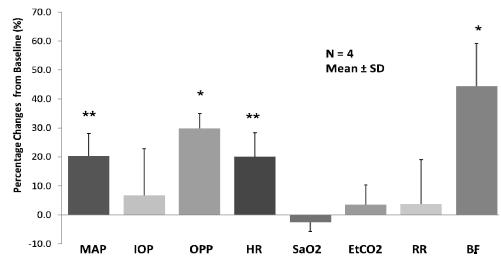


Figure 2. Group-averaged % changes of mean arterial pressure (MAP), intraocular pressure (IOP), ocular perfusion pressure (OPP), heart rate (HR), oxygen saturation (SaO₂), end-tidal CO₂ (EtCO₂), respiration rate (RR), and blood flow (BF) as a result of isometric exercise (* $P < 0.01$ and ** $P < 0.05$).