Published in final edited form as:

Exp Eye Res. 2013 July ; 112: 118–124. doi:10.1016/j.exer.2013.04.003.

MRI Study of Cerebral, Retinal and Choroidal Blood Flow Responses to Acute Hypertension

Guang Li^{1,3}, Yen-Yu I. Shih^{1,*}, Jeffrey W. Kiel², Bryan De La Garza¹, Fang Du¹, and Timothy Q. Duong^{1,2,3,4,5}

¹Research Imaging Institute, University of Texas Health Science Center

²Department of Ophthalmology, University of Texas Health Science Center

³Department of Radiology, University of Texas Health Science Center

⁴Department of Physiology, University of Texas Health Science Center

⁵South Texas Veterans Health Care System

Abstract

Blood flow (BF) in many tissues is stable during significant fluctuations in systemic arterial blood pressure or perfusion pressure under normal conditions. The regulatory mechanisms responsible for this non-passive BF behavior include both local and neural control mechanisms. This study evaluated cerebral BF (CBF), retinal BF (RBF) and choroidal BF (ChBF) responses to acute blood pressure increases in rats using magnetic resonance imaging (MRI). A transient increase in blood pressure inside the MRI scanner was achieved by mechanically inflating a balloon catheter to occlude the descending aorta near the diaphragm. We verified the rat model of mechanical occlusion and MRI approach by first measuring blood-flow regulatory responses to changing BP in the brain under normoxia and hypercapnia where the phenomenon is well documented. Retinal and choroidal blood-flow responses to transient increased arterial pressure were then investigated. In response to an acute increase in blood pressure, RBF exhibited autoregulatory behavior and ChBF exhibited baroregulation similar to that seen in the cerebral circulation. This approach may prove useful to investigate retinal and choroidal vascular dysregulation in rat models of retinal diseases with suspected vascular etiology.

Keywords

cASL MRI; retina; choroid; blood pressure; blood flow; baroregulation; autoregulation

Introduction

Blood flow (BF) in many tissues is relatively stable during fluctuations in systemic arterial blood pressure (BP) or perfusion pressure (PP) under normal conditions. The regulatory

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Correspondence: Timothy Q Duong, Ph.D. (duongt@uthscsa.edu), Research Imaging Institute, University of Texas Health Science Center at San Antonio, 8403 Floyd Curl Dr, San Antonio, TX 78229, Tel: 210-567-8120, Fax: 210-567-8152.

*Present address: Department of Neurology, Biomedical Research Imaging Center, University of North Carolina at Chapel Hill
Guang Li and Yen-Yu I. Shih contributed to this study equally.

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mechanisms responsible for this non-passive BF behavior include both local control mechanisms and neural control mechanisms in tissues receiving autonomic innervation. In circulations lacking autonomic innervation such as the retinal circulation, local control mechanisms are solely responsible for maintaining BF when BP or PP changes, a phenomenon known as autoregulation. In circulations with autonomic innervation such as the cerebral and choroidal circulations, neural and local control mechanisms interact and their relative contributions in maintaining BF are difficult to discern, so the term baroregulation has been used in lieu of autoregulation (Schmetterer and Kiel, 2012).

Although MRI has not yet been used to study retinal and choroidal BF responses to changes in BP or PP in rats, MRI has been used for many years to study cerebral BF (CBF) and more recently to study: i) retinal and choroidal BF in vivo (Li et al., 2012; Muir and Duong, 2011b), ii) retinal and choroidal responses to inspired gas and light stimuli (Muir and Duong, 2011a, b; Shih et al., 2011a; Shih et al., 2012), iii) chorioretinal BF and blood-oxygenation-level-dependent (BOLD) responses to a pharmacological challenge (Shih et al., 2011b), and iv) retinal and choroidal BF in animal models of retinal degeneration (Li et al., 2012; Muir et al., 2012a), glaucoma (Lavery et al., 2012) and diabetic retinopathy (Muir et al., 2012b).

Although rodents are widely used as models of retinal diseases, BF studies in rats are sparse and simultaneous RBF and ChBF responses to changing BP or PP are rare because of the technical difficulties involved. To assess RBF and ChBF BP responses in rats using MRI in the present study, a transient increase in BP inside the scanner was achieved by mechanically inflating a balloon catheter to occlude the descending aorta near the diaphragm (Cividjian et al., 2002; Kiel, 1999). This method can induce transient hypertension above the occluder without pharmacologic manipulation that would confound the vascular responses being investigated. This approach also allows repeated manipulation of BP.

To verify the rat model of mechanical occlusion and the MRI approach, BF baroregulation was first studied in the brain where the phenomenon is well documented. BF baroregulation in the brain was also measured under hypercapnia (5% CO₂ in air), known to impair cerebral baroregulation (Harper, 1966; Kaiser et al., 2005), in order to determine the sensitivity of this approach. Retinal and choroidal BF responses to transient increased arterial pressure were then investigated under normocapnic conditions.

Methods

Animal preparation

Animal experiments were performed with IACUC approval. At the end of the experiments, all animals were euthanized by an overdose of anesthetic and cervical dislocation without regaining consciousness.

- i. CBF study (n = 6): Rats were anesthetized with 1.1~1.2% isoflurane, paralyzed with pancuronium bromide (4 mg/kg first dose, 4 mg/kg/hr, i.p.) and mechanically ventilated during normocapnia (air or 30% O₂) or during hypercapnia (5–7.5% CO₂ mixed with 30% O₂, respectively). A stable plane of anesthesia was maintained, and blood pressure and heart rate (derived from the BP recording) were within normal limits (100–132 mmHg and 370–430 bpm) before and between blood pressure manipulations. BP was recorded continuously (BioPac, MP150) from a transducer (Biopac TSD104A) connected to a PE-50 cannula placed in the right axillary artery as an index of BP at the entry to the cerebral and ocular circulations. The respirator was adjusted so that arterial oxygen saturation (STARR Life Sciences, MouseOx Plus) was > 90% and expired CO₂ (Surgivet™ V9004) was

35–40 mmHg throughout the experiments. Body temperature was maintained at 36.5–37.2° C via a feedback controlled heating pad (Digi-Sense Temperature Controller R/S). BP was modulated by a balloon catheter placed in the descending aorta near the diaphragm via the right femoral artery. Cephalic BP increases were achieved by partially or completely inflating the balloon and redirecting blood flow from the lower to the upper body.

- ii. Ocular BF study (n = 5): The animals were prepared and monitored following the same procedures as the CBF study. The ocular blood flow experiments were only conducted during normocapnia (30% O₂).

MRI methods

MRI studies were performed on an 11.7 Tesla Bruker Biospec (Billerica, MA). For the CBF study, a surface coil (internal diameter = ~2 cm) with active decoupling and a separated butterfly neck coil for continuous arterial spin labeling (cASL) (Duong et al., 2000; Muir and Duong, 2011b; Shen et al., 2004; Shen et al., 2003) were used. CBF MRI was acquired using 5-slice cASL with echo-planar-imaging readout, field of view = 22.4×22.4 mm, repetition time = 3 s, echo time = 10.2 ms, labeling duration 2.9 s, and resolution = 175×175×1500 μm. Modulation paradigm was OFF-ON-OFF. The first OFF period (2 min, 20-pair non-labeled and labeled images) was baseline and the ON period (1 min, 10-pair images) was BP elevation period. Multiple trials were performed on each rat and a 10~15 min break was given between trials. A total of 23 trials during normocapnia and 21 trials during hypercapnia were performed on six rats (3~5 trials in each rat under each of the hypercapnia and normocapnia conditions).

For the ocular BF study, an eye coil (internal diameter = 1 cm) was used for retinal imaging. BF MRI of a single axial slice bisecting the optic nerve head was acquired using 4-segment gradient-echo, inversion-recovery cASL with echo-planar-imaging readout, field of view = 7×7 mm, repetition time = 4 s, echo time = 12.8 ms, and inversion delay = 2.1 s, resolution = 47×47×1000 μm. An inversion-recovery pulse was used to suppress vitreous signals to improve sensitivity (Shen and Duong, 2011). Labeling duration was applied during the inversion delay period. M₀ images were acquired using gradient-echo planar imaging with the same parameters as above except that repetition time = 10 s. One trial consisted of continuous BF measurements during baseline for 320 s (10-pair non- and labeled images) and during elevated BP for 320 s (10-pair non- and labeled images). Multiple trials were performed on each rat with a 10~15 min break between trials. A total of 20 trials were performed on five rats (3 ~ 5 trials in each rat).

Data Analysis

MRI data were acquired in time series and coregistered using Statistical Parametric Mapping 5 (SPM5) software. MRI analysis was performed using Stimulate 6 (University of Minnesota). The cerebrum was manually segmented in each set of 5-slice CBF images and the mean CBF value recorded.

For the retina, the curved retinal and choroidal layers were linearized using custom Matlab codes (Cheng et al., 2006). After motion correction and alignment of linearized labeled, non-labeled and M₀ images, BFs were then calculated based on the aligned linearized images. A BF profile was plotted across retina thickness of one retina image (Li et al., 2012; Muir and Duong, 2011b). Reported BF values were RBF and ChBF peak values on the BF profiles.

The brain and retina BF images in units of ml blood/g tissue/min were obtained using equations $S_{BF} = \lambda/T_1 [(S_{NL}-S_L)/(S_L + (2\alpha - 1)S_{NL})]$ (Duong et al., 2000; Muir and Duong, 2011b; Shen et al., 2004; Shen et al., 2003) and $S_{BF} = \lambda/T_1 [(S_{NL}-S_L)/2\alpha M_0(1-e^{-LD/T_1})]$

(Shen et al., 2005), respectively, where S_{NL} and S_L are signal intensities of the non-labeled and labeled images, respectively. λ , the water tissue-blood partition coefficient, of 0.9 was used for both the brain and retina (λ has not been reported for the retina or choroid) (Herscovitch and Raichle, 1985). The labeling efficiency α was previously measured to be 0.7 (Muir et al., 2008). The brain T_1 at 11.7 Tesla was 2 sec (de Graaf et al., 2006). The retina and choroid T_1 at 11.7 Tesla was 2.1 sec (Chen et al., 2008).

For each trial in the brain or the eye, mean BF and BP during the baseline and the occlusion periods were measured. ΔBF and ΔBP were the absolute differences between the corresponding measures during these two periods, and they were denoted as ΔCBF in the brain study, and ΔRBF (retina) and $\Delta ChBF$ (choroid) in the eye study. ΔBF is the mean BF over the entire occlusion period and therefore, takes into consideration the total baroregulatory/autoregulatory response during the entire period. The analysis was performed for each individual trial.

Statistical Analysis

All statistics were performed in STATA® 11. The Wilcoxon signed-rank test was used to compare medians to zero and for paired data. Wilcoxon rank-sum test was used to compare the medians of two groups. The trend of BF change with respect to BP changes were carefully examined in scatter plots of absolute BP and BF to ensure that all trials showed changes of similar direction and ratio. Simple linear regression was used to fit trend lines in the scatter plots of ΔCBF , ΔRBF and $\Delta ChBF$ versus ΔBP . The significance of the individual regression coefficients were evaluated using the F-test. Also, for each trial, trend lines were fitted to the BF time course during the BP elevation period and the slopes were tabulated. Comparisons between the slopes during the normocapnia and hypercapnia conditions in the brain and between the slopes in the retinal and choroidal vasculatures were conducted. All statistical tests were performed at the significance level of 0.05 (two-sided) with Bonferroni adjustment as needed.

Results

The physiological parameters of the brain and eye experiments at baseline and during BP elevation are summarized in Table 1. Baseline BP and HR were similar between groups and changed in a similar manner during the aortic occlusion (i.e., BP increased and HR decreased significantly). CBF increased significantly during BP elevation under both normocapnic and hypercapnic conditions ($P < 0.05$). Baseline CBF during hypercapnia was higher compared to that during normoxia ($P < 0.05$). ChBF also increased significantly during BP elevation, but RBF did not.

Cerebral blood flow

Typical mean baseline CBF images, regions of interest (ROI) and traces of BP, HR, and CBF as well as the mean CBF traces from all trials during normocapnia are depicted in Figure 1. BP and CBF were elevated immediately after inflating the balloon. HR decreased, presumably due to the baroreflex response to elevated BP. CBF then declined toward baseline after its initial increase as BP remained elevated. BP, and CBF (but not HR) undershot baseline immediately after deflating the balloon occluder.

A trend line was fitted onto the CBF time course during BP elevation, with the slope of the fitted line showing the rate of BF change. BF decreased faster during normocapnia (Figure 2A) than during hypercapnia (Figure 2B). Figure 2C plots the median values for the slopes of CBF returning toward baseline during normocapnia and during hypercapnia. The slopes did not vary as a function of BF (data not shown) but they were significantly different from

zero ($p = 0.0001$ and 0.0012 ; Wilcoxon signed-rank test) and from each other ($p = 0.047$, Wilcoxon rank-sum test). In other words, CBF during BP elevation returned toward baseline during both conditions but at a faster rate during normocapnia than hypercapnia.

During normocapnia, the slope of the regression line for ΔCBF vs. ΔBP was not different from 0 ($p = 0.485$) (Figure 3A). By contrast, during hypercapnia (Figure 3B), ΔCBF increased linearly with ΔBP ($p < 0.0001$, regression coefficient = $0.00867 \text{ ml/g/min/mm Hg}$). The mean ΔCBF during normocapnia ($0.16 \pm 0.057 \text{ ml/g/min}$) was also significantly lower ($p = 0.003$, Wilcoxon signed-rank test) than the mean ΔCBF during hypercapnia ($0.3 \pm 0.192 \text{ ml/g/min}$).

The ΔBP ranges differed between normocapnia and hypercapnia. Unfortunately, it was difficult to obtain graded BP elevations (particularly for pressure changes $< 20 \text{ mm Hg}$) with the balloon catheter. It is possible that the hypercapnia may have differentially dilated different tissues and/or shifted the baroreflex gain, which may have made it harder to achieve graded pressure changes. Nonetheless, the ΔCBF versus ΔBP regression lines for normocapnia and hypercapnia were significantly different even if the data for ΔBP below 20 mmHg were not included.

Ocular blood flow

A typical baseline ocular BF image, its BF profile across the retinal thickness and traces of BP, HR, RBF and ChBF as well as the mean RBF and ChBF traces from all trials are shown in Figure 4. BP was elevated and remained stable during the occlusion period. The mean RBF for the initial 128 seconds of the BP elevation was significantly higher than the baseline, indicating that the RBF increased transiently, although the mean RBF for the entire BP elevation was not significantly different from baseline (Table 1). Hence, RBF showed a trend of returning toward baseline. Similarly, at the onset of BP elevation, ChBF increased initially but then also declined toward baseline.

Trend lines were fitted to the ChBF and RBF time courses during the BP elevation (Figure 5A). ChBF and RBF returned towards baseline at median rates of $-5.51 \times 10^{-3} \text{ ml/g/min/sec}$ and $-1.132 \times 10^{-3} \text{ ml/g/min/sec}$, respectively (Figure 5B). As with CBF, neither slope varied as a function of BP (data not shown) and both were significantly less than 0 ($p = 0.0001$ and 0.0187 ; Wilcoxon signed-rank test), and significantly different from each other ($p = 0.004$, Wilcoxon matched-pairs signed-rank test).

The slopes of the trend lines of ΔRBF and ΔChBF vs. ΔBP were not significantly different from zero ($p = 0.39$ and 0.32) as shown in Figure 6, indicating the absence of correlation between BF and BP changes in both the retinal and choroidal circulations.

Discussion

This study reports the use of BF fMRI to study BF responses to acute BP increases in the rat cerebral, retinal and choroidal circulations. All three circulations exhibited non-passive BF responses to increased BP indicative of active regulatory mechanisms.

During normocapnia, BP elevation elicited an initial rise in CBF that then returned toward baseline as BP remained elevated. The ΔCBF vs. ΔBP relationship for the entire BP elevation period was also not correlated (i.e., BF was stable over a range of BP above baseline, Figure 3A). This non-passive BF behavior indicates an active regulatory process but the underlying mechanisms are unclear. The cerebral circulation receives both sympathetic and parasympathetic neural inputs (MacKenzie et al., 1979; Morita et al., 1994; Talman and Dragon, 2000) and the bradycardia during the BP elevation suggests baroreflex

modulation of one or both arms of the autonomic nervous system occurred, which may have influenced the CBF response. Local control mechanisms were also probably involved since the hypercapnia-induced cerebral vasodilation during baseline and the attenuated return of CBF towards control during BP elevation are consistent with direct vascular responsiveness needed for metabolic local control, and the increased vascular resistance during elevated BP is consistent with the myogenic response. Thus, because both neural control as well as local control mechanisms were possibly operative, the behavior cannot be viewed as “autoregulation” (i.e., intrinsic to the tissue itself) in the traditional sense, and so the term baroregulation is more appropriate.

The purpose of the CBF experiments was to validate the aortic occlusion model and the cASL MRI methodology in the rat, not to define the underlying mechanisms. Similar non-passive CBF responses to BP elevation by aortic occlusion have been observed in cats, dogs (Busija et al., 1980) and monkeys (Yoshida et al., 1966) suggesting that the choice of species was reasonable. Similar non-passive CBF responses to BP have also been reported in studies using different anesthetics (Busija et al., 1980) and a variety of different BF measuring techniques (Busija et al., 1980; Yoshida et al., 1966). Different anesthetics have different effects on baroregulation. Isoflurane, in particular, is a known vasodilator that has been shown to mildly impair cerebral baroregulation in a dose-dependent manner in rats (Hoffman et al., 1991). Thus, it is possible that the rate of return toward baseline for CBF during elevated BP under isoflurane may have been slower than under unanesthetized conditions or with other anesthetics. In spite of the potentially underestimated rate of return toward baseline for CBF, however, the similar CBF results across species, anesthetics and BF measuring techniques lends credence to the ocular BF results that are novel. To our knowledge, simultaneous RBF and ChBF cASL MRI measurements during BP elevation in the rat have not been performed previously.

As in the cerebral circulation, BP elevation elicited initial increases in RBF and ChBF that returned toward baseline as BP remained elevated, and the Δ BF vs. Δ BP relationships were not correlated. Here again, this non-passive BF behavior is indicative of an active regulatory process. In the case of the RBF, the lack of retinal autonomic innervation points to local control associated with autoregulation (metabolic, myogenic and shear stress local control mechanisms). In the case of the choroid, which has autonomic innervation, the ChBF behavior could be a mixture of neural and local control, and so the behavior is consistent with baroregulation as was the case with CBF. One caveat regarding the RBF response is that the central retinal artery that supplies the retinal circulation is innervated, which could influence the RBF response. However, the function central retinal artery neural control is unknown. If it participates in the arterial baroreflex (as seems possible), it should cause vasodilation of the central retinal artery during an acute increase in BP, which would further increase RBF rather than the observed return toward baseline that occurred. The same caveat applies to choroidal neural control.

Similar non-passive RBF and ChBF responses to changing BP have been reported for other species (e.g. pigeons, rabbits, cats, pigs, monkeys and humans), with and without anesthesia, and using various blood flow measuring techniques (Alm and Bill, 1973; Chemtob et al., 1991; Kiel, 1994; Reiner et al., 2003; Robinson et al., 1986; Weiter et al., 1973). However, there are relatively few rat eye BF studies, no studies investigating rat RBF responses to changing BP, and only one study of rat ChBF responses to fluctuating BP (Reiner et al., 2010) to our knowledge. In that study, anterior ChBF was measured transclerally with a fiber optic laser Doppler flowmeter and ChBF was relatively stable as BP varied spontaneously from 60 – 140 mmHg; below that range, ChBF was BP-dependent. Consistent with that result, we found ChBF to be relatively stable when BP was increased

mechanically from 114 to 153 mmHg. Additional studies are needed to confirm the RBF results and further corroborate the ChBF results.

Conclusions

In conclusion, we established a rat model in which BP can be manipulated mechanically inside a MRI scanner while simultaneously measuring RBF and ChBF with cASL BF MRI. In response to an acute increase in BP, RBF exhibited autoregulatory behavior and ChBF exhibited baroregulation similar to that seen in the cerebral circulation. In the future, this approach may prove useful to investigate retinal and choroidal vascular dysregulation in rat models for diseases such as glaucoma, diabetic retinopathy and other eye diseases with suspected vascular etiology.

Acknowledgments

Grant support: This work was supported in part by the NIH/NEI (R01 EY014211, EY018855 and EY009702), MERIT Award from the Department of Veterans Affairs, and San Antonio Life Science Institute to TQD and American Heart Association (10POST4290091), CTSA/R11 imaging supplement awards (CTSA-004A and CTSA-008A), and San Antonio Area Foundation to YYIS.

Abbreviations

BF	blood flow
BP	blood pressure
RBF	retinal blood flow
ChBF	choroidal blood flow
LDF	laser Doppler flowmetry
HR	heart rate
cASL	continuous arterial spin labeling
BOLD	blood-oxygenation-level-dependent

References

- Alm A, Bill A. Ocular and optic nerve blood flow at normal and increased intraocular pressures in monkeys (*Macaca irus*): a study with radioactively labelled microspheres including flow determinations in brain and some other tissues. *Experimental eye research*. 1973; 15:15–29. [PubMed: 4630581]
- Busija DW, Heistad DD, Marcus ML. Effects of Sympathetic-Nerves on Cerebral Vessels during Acute, Moderate Increases in Arterial-Pressure in Dogs and Cats. *Circulation Research*. 1980; 46:696–702. [PubMed: 7363418]
- Chemtob S, Beharry K, Rex J, Chatterjee T, Varma DR, Aranda JV. Ibuprofen Enhances Retinal and Choroidal Blood-Flow Autoregulation in Newborn Piglets. *Invest Ophthalmol Vis Sci*. 1991; 32:1799–1807. [PubMed: 2032803]
- Chen J, Wang Q, Zhang J, Yang X, Wang J, Berkowitz BA, Wickline SA, Song SK. In vivo quantification of T1, T2, and apparent diffusion coefficient in the mouse retina at 11.74T. *Magn Reson Med*. 2008; 59:731–738. [PubMed: 18383302]
- Cheng H, Nair G, Walker TA, Kim MK, Pardue MT, Thule PM, Olson DE, Duong TQ. Structural and functional MRI reveals multiple retinal layers. *Proc Natl Acad Sci USA*. 2006; 103:17525–17530. [PubMed: 17088544]

- Cividjian A, Rentero N, McAllen R, Quintin L. A simple method for generating a blood pressure-unit activity relationship for central cardiovascular neurons in the rat. *Exp Physiol*. 2002; 87:535–538. [PubMed: 12481927]
- de Graaf RA, Brown PB, McIntyre S, Nixon TW, Behar KL, Rothman DL. High magnetic field water and metabolite proton T1 and T2 relaxation in rat brain in vivo. *Magn Reson Med*. 2006; 56:386–394. [PubMed: 16767752]
- Duong TQ, Silva AC, Lee SP, Kim SG. Functional MRI of calcium-dependent synaptic activity: cross correlation with CBF and BOLD measurements. *Magn Reson Med*. 2000; 43:383–392. [PubMed: 10725881]
- Harper AM. Autoregulation of cerebral blood flow: influence of the arterial blood pressure on the blood flow through the cerebral cortex. *J Neurol Neurosurg Psychiatry*. 1966; 29:398–403. [PubMed: 5926462]
- Herscovitch P, Raichle ME. What is the correct value for the brain-blood partition coefficient for water? *J Cereb Blood Flow Metab*. 1985; 5:65–69. [PubMed: 3871783]
- Hoffman WE, Edelman G, Kochs E, Werner C, Segil L, Albrecht RF. Cerebral autoregulation in awake versus isoflurane-anesthetized rats. *Anesth Analg*. 1991; 73:753–757. [PubMed: 1952176]
- Kaiser JR, Gauss CH, Williams DK. The effects of hypercapnia on cerebral autoregulation in ventilated very low birth weight infants. *Pediatr Res*. 2005; 58:931–935. [PubMed: 16257928]
- Kiel JW. Choroidal myogenic autoregulation and intraocular pressure. *Exp Eye Res*. 1994; 58:529–543. [PubMed: 7925690]
- Kiel JW. Modulation of choroidal autoregulation in the rabbit. *Exp Eye Res*. 1999; 69:413–429. [PubMed: 10504275]
- Lavery WJ, Muir ER, Kiel JW, Duong TQ. Magnetic resonance imaging indicates decreased choroidal and retinal blood flow in the DBA/2J mouse model of glaucoma. *Invest Ophthalmol Vis Sci*. 2012; 53:560–564. [PubMed: 22205612]
- Li G, De La Garza B, Shih YY, Muir ER, Duong TQ. Layer-specific blood-flow MRI of retinitis pigmentosa in RCS rats. *Exp Eye Res*. 2012; 101:90–96. [PubMed: 22721720]
- MacKenzie ET, McGeorge AP, Graham DI, Fitch W, Edvinsson L, Harper AM. Effects of increasing arterial pressure on cerebral blood flow in the baboon: influence of the sympathetic nervous system. *Pflugers Archiv : European journal of physiology*. 1979; 378:189–195. [PubMed: 107511]
- Morita Y, Hardebo JE, Bouskela E. Influence of cerebrovascular parasympathetic nerves on resting cerebral blood flow, spontaneous vasomotion, autoregulation, hypercapnic vasodilation and sympathetic vasoconstriction. *J Auton Nerv Syst*. 1994; 49(Suppl):S9–14.
- Muir ER, De La Garza B, Duong TQ. Blood flow and anatomical MRI in a mouse model of retinitis pigmentosa. *Magn Reson Med*. 2012a
- Muir ER, Duong TQ. Layer-specific functional and anatomical MRI of the retina with passband balanced SSFP. *Magn Reson Med*. 2011a; 66:1416–1421. [PubMed: 21604296]
- Muir ER, Duong TQ. MRI of retinal and choroidal blood flow with laminar resolution. *Nmr Biomed*. 2011b; 24:216–223. [PubMed: 20821409]
- Muir ER, Renteria RC, Duong TQ. Reduced ocular blood flow as an early indicator of diabetic retinopathy in a mouse model of diabetes. *Invest Ophthalmol Vis Sci*. 2012b; 53:6488–6494. [PubMed: 22915034]
- Muir ER, Shen Q, Duong TQ. Cerebral blood flow MRI in mice using the cardiac-spin-labeling technique. *Magn Reson Med*. 2008; 60:744–748. [PubMed: 18727091]
- Reiner A, Zagvazdin Y, Fitzgerald MEC. Choroidal blood flow in pigeons compensates for decreases in arterial blood pressure. *Experimental eye research*. 2003; 76:273–282. [PubMed: 12573656]
- Robinson F, Riva CE, Grunwald JE, Petrig BL, Sinclair SH. Retinal blood flow autoregulation in response to an acute increase in blood pressure. *Invest Ophthalmol Vis Sci*. 1986; 27:722–726. [PubMed: 3700021]
- Schmetterer, L.; Kiel, J. *Ocular Blood Flow*. Springer; 2012.
- Shen Q, Duong TQ. Background suppression in arterial spin labeling MRI with a separate neck labeling coil. *Nmr Biomed*. 2011

- Shen Q, Fisher M, Sotak CH, Duong TQ. Effect of reperfusion on ADC and CBF pixel-by-pixel dynamics in stroke: Characterizing tissue fates using quantitative diffusion and perfusion imaging. *J Cereb Blood Flow and Metab.* 2004; 24:280–290. [PubMed: 15091108]
- Shen Q, Meng X, Fisher M, Sotak CH, Duong TQ. Pixel-by-pixel spatiotemporal progression of focal ischemia derived using quantitative perfusion and diffusion imaging. *J Cereb Blood Flow and Metab.* 2003; 23:1479–1488. [PubMed: 14663344]
- Shen Q, Ren H, Cheng H, Fisher M, Duong TQ. Functional, perfusion and diffusion MRI of acute focal ischemic brain injury. *J Cereb Blood Flow and Metab.* 2005; 25:1265–1279. [PubMed: 15858531]
- Shih YY, De la Garza BH, Muir ER, Rogers WE, Harrison JM, Kiel JW, Duong TQ. Lamina-specific functional MRI of retinal and choroidal responses to visual stimuli. *Invest Ophthalmol Vis Sci.* 2011a; 52:5303–5310. [PubMed: 21447679]
- Shih YY, Muir ER, Li G, De La Garza BH, Duong TQ. High-Resolution 3D MR Microangiography of the Rat Ocular Circulation. *Radiology.* 2012; 264:234–241. [PubMed: 22523323]
- Shih YYI, Li G, Muir ER, De La Garza BH, Kiel JW, Duong TQ. Pharmacological MRI of the choroid and retina: Blood flow and BOLD responses during nitroprusside infusion. *Magn Reson Med.* 2011b
- Talman WT, Dragon DN. Parasympathetic nerves influence cerebral blood flow during hypertension in rat. *Brain Res.* 2000; 873:145–148. [PubMed: 10915822]
- Weiter JJ, Schachar RA, ERNEST JT. Control of intraocular blood flow.: I. Intraocular pressure. *Invest Ophthalmol Vis Sci.* 1973; 12:327–331.
- Yoshida K, Meyer JS, Sakamoto K, Handa J. Autoregulation of Cerebral Blood Flow - Electromagnetic Flow Measurements during Acute Hypertension in Monkey. *Circulation Research.* 1966; 19:726–738. [PubMed: 4958384]

Figure 1.

CBF protocol. (A) CBF images at baseline and the regions of interest used to tabulate CBF from a typical trial. (B) Traces for BP, HR and CBF before, during and after BP elevation induced by aortic occlusion from a typical trial. The occlusion duration (60 sec) is indicated by the shaded area. (C) Mean traces for all trials during normocapnia and hypercapnia (Error bars: SEM, $n = 23$ for normocapnia and $n = 21$ for hypercapnia).

Figure 2.

CBF responses to acute hypertension from a typical trial during (A) normocapnia and (B) hypercapnia. Trend lines are overlaid on CBF time courses during the hypertensive period. The BP time points are averages over 6-sec intervals to match the cASL MRI temporal resolution used for the brain. (C) A box plot of the BF rates of return toward baseline during the aortic occlusion under normocapnia and hypercapnia. The median of the slopes during both conditions were significantly below zero ($p = 0.0001$ and 0.0012). The normocapnia median rate was significantly more negative than the hypercapnia median rate ($p = 0.047$).

Figure 3.

(A) Scatter plot of ΔBF versus ΔBP during normocapnia. ΔBF and ΔBP were not correlated ($p = 0.485$). (B) Scatter plot of ΔBF versus ΔBP during hypercapnia. ΔBF and ΔBP were positively correlated ($p < 0.0001$). The mean ΔCBF during normocapnia (0.16 ± 0.057 ml/g/min) was significantly lower ($p = 0.003$) than ΔCBF during hypercapnia (0.3 ± 0.192 ml/g/min).

Figure 4.

Eye BF protocol. (A) Rat eye BF image at baseline and the region of interest used to tabulate RBF and ChBF from a typical trial. (B) The BF profile across the retinal thickness averaged over the ROI shown in A. (C) Traces for BP, HR and RBF and ChBF before and during BP elevation induced by aortic occlusion in a typical trial. The occlusion duration (320 sec) is indicated by the shaded area. (D) Mean RBF traces for all trials. (E) Mean ChBF traces for all trials. (Error bars: SEM, $n = 20$)

Figure 5.

(A) RBF and ChBF responses to acute hypertension. Trend lines are overlaid on RBF and ChBF time courses during the aortic occlusion. The BP time points are averages over 32-sec intervals to match the cASL MRI temporal resolution used for the eye. (B) A box plot of the choroidal and retinal BF rates of return toward baseline during the aortic occlusion. The median slopes for RBF and ChBF were significantly less than zero ($p = 0.0187$ and 0.0001). The RBF median rate was significantly more negative than the ChBF median rate ($p = 0.004$).

Figure 6. Scatter plots of (A) ΔRBF versus ΔBP and (B) $\Delta ChBF$ versus ΔBP . Data points with the same symbol were from trials in the same animal. The slopes of the trend lines were not significantly different from 0 ($p = 0.39$ and 0.32 , respectively).

Summary of blood pressure, heart rate, and blood flows (mean ± SEM) during baseline (120 sec for brain and 320 sec for eye prior to aortic occlusion) and during BP elevation (60 sec for brain and 320 sec for eye).

Table 1

(a) Brain	Normocapnia			Hypercapnia		
	BP (mm Hg)	HR (beat/min)	CBF (ml/g/min)	BP (mm Hg)	HR (beat/min)	CBF [§] , [‡] (ml/g/min)
Baseline	116 ± 2.9	394 ± 4.6	0.72 ± 0.04	122 ± 2.2	396 ± 4.8	1.30 ± 0.08
BP Elevation	153 ± 3.8 [§]	363 ± 4.0 [§]	0.87 ± 0.05 [§] , [‡]	151 ± 4.6 [§]	367 ± 3.9 [§]	1.63 ± 0.10 [§] , [‡]
(b) Eye						
	Normocapnia					
	BP (mm Hg)	HR (beat/min)	RBF (ml/g/min)	ChBF (ml/g/min)		
Baseline	114 ± 2.2	419 ± 4.7	0.77 ± 0.05	6.32 ± 0.39		
BP Elevation	153 ± 2.9 [§]	396 ± 5.4 [§]	0.84 ± 0.09	7.90 ± 0.39 [§]		

[§] significant differences between the baseline and BP elevation period (Bonferroni adjusted p value < 0.05)

[‡] significant differences between normocapnia and hypercapnia (Bonferroni adjusted p value < 0.05)