368 Glaucoma Pharmacology and clinical studies
Tuesday, May 06, 2014 3:45 PM–5:30 PM
S 310A-D Paper Session
Program #/Board # Range: 3546–3552
Organizing Section: Glaucoma

Program Number: 3546
Presentation Time: 3:45 PM–4:00 PM
Dissection of a QTL Locus on Mouse Proximal Chromosome 5 that Modulates Intraocular Pressure (IOP) leads to Identification of a Potential New Drug Target for Glaucoma
Shankar Swaminathan[1], Hong Lu[1, 2], Janey L. Wiggs[3], Robert W. Williams[2], Lu Lu[2], Monica M. Jablonski[1, 2]. [1]Ophthalmology, Hamilton Eye Institute, The University of Tennessee Health Science Center, Memphis, TN; [2]Anatomy & Neurobiology, The University of Tennessee Health Science Center, Memphis, TN; [3]Ophthalmology, Harvard Medical School, Massachusetts Eye and Ear Infirmary, Boston, MA.
Purpose: Current IOP lowering therapies are used on a trial and error basis without a pharmacogenomic rationale, leading to variability in drug effect. Within our large high-throughput gene screening, we identify genetic modifiers of IOP using the enlarged BXD glaucoma murine reference panel in combination with human GWAS glaucoma cohorts. Our objective in the study was to identify new gene loci modulating IOP using systems genetics and design new drug targets for personalized glaucoma therapy.
Methods: We acquired IOP measurements for parents and 80 progeny BXD lines at 1–2, 3–5, 6–9, 10–13 and >13 months of age, using a TONOLAB. Conventional arrays and RNA-seq data were used to estimate gene expression from eyes of parents and progeny. IOP datasets were mapped using GeneNetwork (www.genenetwork.org). Candidate genes for high IOP/ primary open angle glaucoma (POAG) were nominated using the following criteria: (1) genes are located within confidence intervals of QTLs; (2) genes have coding differences segregating among progeny; (3) genes are expressed in the eye, and are associated with cis-expression QTL (eQTL); (4) expression of transcripts covary with IOP; (5) genes have a plausible biological link to IOP and glaucoma; (6) genes are close to linkage peaks in the GLAUGEN and NEIGHBOR human POAG GWAS studies; and (7) genes are druggable. Subsequently, a druggable gene drug target and a small molecule drug were selected for further studies. The IOP lowering effect on high and low expresser BXD strains of the selected gene was studied (n=6) and the pharmacodynamic profile computed.
Results: IOP varied from 9.3±0.8 to 21.8±1.7 mmHg across BXDs. We identify a robust eQTL on proximal Chr 5 in BXD mice strains aged 10–13 mo. Within this QTL, candidates were nominated and the best SNP in each candidate were identified using human data from the GLAUGEN/NEIGHBOR GWAS data. Within the candidates, we identified a druggable gene target (a cation channel; p-value= 0.007526) that regulated ion transport in the eye. A single topical dose of the cation channel blocker reduced IOP by >4mmHg (>20%) in high BXD expressers from baseline within 3 h and returned to baseline after 6 h.
Conclusions: We have identified potential candidate genes that modulate IOP and further evaluated the suitability of a druggable gene target for personalized POAG therapy.
Commercial Relationships: Shankar Swaminathan, 61/868,991 (P), 61/869,498 (P); **Hong Lu**, None; **Janey L. Wiggs**, None; **Robert W. Williams**, None; **Lu Lu**, None; **Monica M. Jablonski**, 61/868,991 (P), 61/869,498 (P)
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Program Number: 3547
Presentation Time: 4:00 PM–4:15 PM
Ocular hypotensive effects of the K_{ATP} channel opener cromakalim in murine and human experimental model systems
Uttio Roy Chowdhury, Cindy K. Bahler, Bradley H. Holman, Michael P. Fautsch. Ophthalmology, Mayo Clinic, Rochester, MN.
Purpose: Studies from our laboratory have shown that the K_{ATP} channel opener diazoxide lowers intraocular pressure (IOP) by activating the SUR2B/K_{ir}6.2 subunit containing channels. In this study, we evaluated the IOP lowering ability of the broad spectrum K_{ATP} channel opener cromakalim (CKL) which activates both SUR2B/K_{ir}6.2 and SUR2A/K_{ir}6.2 subunit containing channels. Efficacy of combination therapy with CKL and latanoprost free acid (LFA) was also evaluated.
Methods: Human anterior segment pairs (n=10, mean age 72.5±15.1, range 52 to 88 years) were placed in perfusion organ culture and treated with CKL (0.02 μM, 0.2 μM, and 2 μM) or vehicle (DMSO). In vivo IOP-lowering effects of topically administered CKL (5 mM in 10% cremophor EL), either alone or in combination with LFA (0.005% in PBS, n=10), was evaluated in wild type C57BL/6 mice using a handheld rebound tonometer. Subunit specificity of CKL was studied in $K_{ir}6.2^{(-/-)}$ mice (n=10). Tissue morphology of all eyes treated with CKL, LFA and respective vehicles was imaged by transmission electron microscopy and evaluated by at least two independent masked observers.
Results: Cromakalim (2 μM) increased outflow facility in human anterior segments compared to baseline (0.13±0.02 to 0.20±0.04 μl/min/mmHg, n=10, P<0.001). Outflow facility was unchanged in the vehicle treated segments (0.18±0.06 to 0.17±0.05 μl/min/mmHg, n=10, P=0.9). No change in outflow facility was observed with cromakalim added at 0.02 or 0.2 μM. In vivo, mouse eyes treated with CKL alone showed a 20.3% reduction in IOP compared to control (13.63±0.16 to 17.1±0.35 mmHg, n=5, P<0.001). When CKL was combined with LFA, IOP decreased by an additional 71% compared to mice eyes treated with CKL alone (n=10, P<0.001). Treatment of $K_{ir}6.2^{(-/-)}$ mice with CKL did not show any reduction in IOP (16.09±0.26 mmHg to 16.09±0.29 mmHg, n=10, P>0.05). Histologic analysis of treated and control eyes showed no major disruptions of the inner and outer wall of Schlemm's canal, comparable cell numbers, and extracellular matrix integrity throughout the trabecular meshwork.
Conclusions: The K_{ATP} channel opener CKL is a potent ocular hypotensive agent that specifically acts through the $K_{ir}6.2$ subunit containing K_{ATP} channels. The mechanism of action of CKL is distinct to that of LFA. The K_{ATP} channel opener CKL has potential as an ocular hypotensive agent either alone or in combination with LFA.
Commercial Relationships: Uttio Roy Chowdhury, None; **Cindy K. Bahler**, None; **Bradley H. Holman**, None; **Michael P. Fautsch**, None
Support: NIH grant EY21727; Research to Prevent Blindness; Mayo Foundation

Program Number: 3548
Presentation Time: 4:15 PM–4:30 PM
Preclinical Evaluation of ENV515 (travoprost) Intracameral Implant - Clinical Candidate for Treatment of Glaucoma Targeting Six-Month Duration of Action

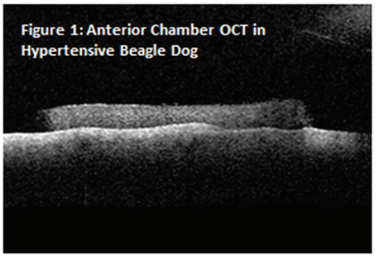
Tomas Navratil[1], Andres Garcia[1], Janet Tully[1], Benjamin Maynor[1], Iqbal Ike K. Ahmed[4], Donald L. Budenz[5], Richard A. Lewis[2], Steven L. Mansberger[3], Brian C. Gilger[6], Benjamin R. Yerxa[1]. [1]Envisia Therapeutics, Research Triangle Park, NC; [2]Sacramento Eye Consultants, Sacramento, CA; [3]Devers Eye Institute, Portland, OR; [4]University of Toronto, Toronto, ON, Canada; [5]University of North Carolina, Chapel Hill, NC; [6]North Carolina State University, Raleigh, NC.

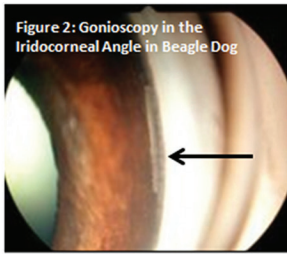
Purpose: Prostaglandin analogues (PGA) are the most prescribed class of therapies for glaucoma in the US but possess several shortcomings: low adherence, hyperemia, and fluctuation in ocular drug levels and intraocular pressure (IOP). The purpose of this work was to evaluate the efficacy, duration of action, and safety/tolerability of the ENV515 (travoprost) Intracameral Implant experimental therapy prior to further preclinical and clinical development. ENV515 is a biodegradable polymer drug delivery system using an extended release formulation of the PGA travoprost. ENV515 is being developed with the aim to address the shortcomings of the topical PGA therapies.

Methods: We used PRINT® technology to fabricate ENV515 to fit the anatomy of the human iridocorneal angle and allow administration via acceptably-sized needle. We used hypertensive and normotensive Beagle dogs using a modified McDonald-Shadduck scale to evaluate safety and tolerability over a period of 24 weeks in vivo. The in vivo location of the implant was imaged via anterior chamber OCT and Gonioscopy exams. IOP was evaluated in non-sedated animals.

Results: In vitro, the extended release of travoprost from ENV515 occurred over a period of 180 days. The implant administrations were conducted in Beagle dogs by intracameral injections via a custom injector and resulted in 100% success rate for implant delivery. Gonioscopy and anterior chamber OCT imaging showed stability without movement in the iridocorneal angle in hypertensive Beagle dogs (Figures 1 and 2). The baseline IOP in hypertensive Beagle dog study was 23.4±1.0 mmHg (mean±SEM, n=6 eyes). The mean decrease in intraocular pressure was 7.2±0.5 mmHg or 30±2% change from baseline IOP over 24 week treatment period ($p<0.001$). Only minor and transient ocular irritation occurred due to the insertion procedure. Notably, there was lower incidence of hyperemia compared to topical TRAVATAN Z. Similar outcomes were observed in a replicatory study in normotensive Beagle dogs.

Conclusions: ENV515 demonstrated robust, sustained IOP-lowering effect for 24 weeks following single implantation via intracameral injection with acceptable safety and tolerability in hypertensive and normotensive Beagle dogs. ENV515 preclinical safety and tolerability profile supports advancing ENV515 into clinical studies in glaucoma patients.





Commercial Relationships: Tomas Navratil, Envisia Therapeutics (E); **Andres Garcia**, Envisia Therapeutics (E); **Janet Tully**, Envisia Therapeutics (E); **Benjamin Maynor**, Envisia Therapeutics (E); **Iqbal Ike K. Ahmed**, Envisia Therapeutics (C); **Donald L. Budenz**, None; **Richard A. Lewis**, Envisia Therapeutics (C); **Steven L. Mansberger**, Envisia Therapeutics (C); **Brian C. Gilger**, Envisia Therapeutics (C); **Benjamin R. Yerxa**, Envisia Therapeutics (E)

Program Number: 3549
Presentation Time: 4:30 PM–4:45 PM
Efficacy of Latanoprostene Bunod Ophthalmic Solution 0.024% Compared With Timolol Maleate Ophthalmic Solution 0.5% in Lowering IOP over 24 hours in Subjects With Open Angle Glaucoma or Ocular Hypertension (CONSTELLATION)

John H. Liu[1], Jason L. Vittitow[2], Quintus Ngumah[2], Robert N. Weinreb[1]. [1]Dept of Ophthalmology and Hamilton Glaucoma Center, Univ of California, San Diego, La Jolla, CA; [2]Bausch & Lomb, Madison, NJ.

Purpose: To compare the effect of latanoprostene bunod (LBN) 0.024% QD with timolol maleate 0.5% BID in reducing 24-hour intraocular pressure (IOP) in subjects with open angle glaucoma (OAG) or ocular hypertension (OHT).

Methods: This was a randomized, single-center, open-label, 2-period, 8-week study with crossover at 4 weeks. Twenty subjects (43–82 years) with a baseline IOP at least 22 mmHg in at least 1 eye and less than 36 mmHg in both eyes and a diagnosis of OAG or OHT were included. Subjects were housed in a sleep laboratory for 24 hours and a baseline IOP profile was created. IOP of both eyes was measured with a pneumatonometer every two hours in the sitting and supine positions from 8AM to 10PM, and in the supine position only from 12AM to 6AM. During the first period of the study subjects were randomized 1:1 to either of 2 treatment sequences: LBN 0.024% instilled in both eyes at 8PM or timolol maleate 0.5% instilled twice a day at 8AM and 8PM. After four weeks of treatment, subjects were housed in the sleep laboratory for a second 24 hour period IOP measurement. At the end of the 24 hours, subjects were crossed over to receive the comparator treatment, which initiated period 2. After four weeks of the period 2 treatment, subjects were housed in the sleep laboratory for a third 24 hour IOP measurement. The mean IOP from both periods for the 2 treatment groups (LBN 0.024% QD and timolol maleate 0.5% BID) were compared using a Mixed Model Repeated Measures analysis of variance (ANOVA) model, during the diurnal, nocturnal, and 24 hour periods.

Results: Mean change from baseline in IOP (mmHg) was 3.9±0.28 for latanoprostene bunod treated eyes and 2.4±0.29 for timolol treated eyes during the diurnal period; 2.75 ± 0.45 for latanoprostene bunod and 0.2±0.46 for timolol during the nocturnal period; and 3.5 ± 0.24 for latanoprostene bunod and 1.7±0.25 for timolol during the entire 24 hour period.

Conclusions: In this group of open angle glaucoma/ocular hypertensive patients, LBN 0.024% was shown to be superior to timolol with regard to IOP lowering during the entire 24 hour period measured ($p<0.05$), suggesting that treatment with LBN 0.024% may provide more effective and better sustained diurnal and nocturnal IOP reduction.

Commercial Relationships: John H. Liu, Aerie (F), Alcon (F), Allergan (F), Bausch & Lomb (F), NASA (F), Sensimed (F); **Jason L. Vittitow**, Bausch & Lomb (E); **Quintus Ngumah**, Bausch & Lomb (E); **Robert N. Weinreb**, Aerie (F), Alcon (C), Allergan (C), Amakem (C), Bausch & Lomb (C), Carl Zeiss-Meditec (C), Genentech (F), Heidelberg Engineering (F), Konan (F), Lumenis (F), National Eye Institute (F), Nidek (F), Optovue (F), Topcon (C)
Support: Bausch & Lomb 803

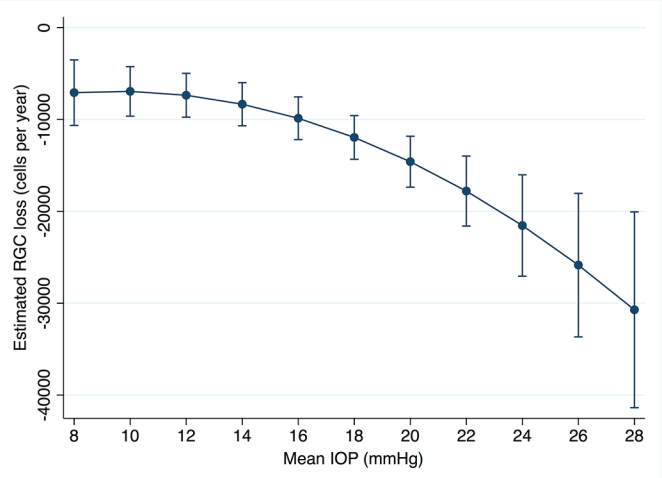
Clinical Trial: NCT01707381

Program Number: 3550
Presentation Time: 4:45 PM–5:00 PM
Observation periods of 1 year for clinical trials of neuroprotective agents in glaucoma are feasible
David F. Garway-Heath[1], Haogang Zhu[1, 2], David P. Crabb[2]. [1]Institute of Ophthalmology, University College London, London, United Kingdom; [2]Optometry and Visual Science, City University London, London, United Kingdom.
Purpose: Before the United Kingdom Glaucoma Treatment Study (UKGTS), a placebo-controlled treatment trial for manifest glaucoma, clinical trials in glaucoma with a visual field (VF) outcome typically had observation periods of 5 years or longer. The UKGTS reported a significant outcome with a 2-year observation period, with the difference between treatment arms evident after only 12 months. The UKGTS was designed to maximize the precision of estimates of progression rate (speed). In this study, the UKGTS data were used as the basis for modelling a trial of neuroprotection.
Methods: The assumed study design is a placebo-controlled trial of a neuroprotective agent, with all patients taking latanoprost in addition. The rates of progression from the eye with the worst VF loss at baseline in the latanoprost-treated arm of the UKGTS, with at least 6 months of follow-up, were used for modelling. For patients with less than 12 months follow-up, the rate for the available series was used. The modelling of the UKGTS VF data identified the outcome with greatest power to separate treatment groups as the mean rate of loss at the 10 fastest deteriorating locations in each eye. Progression rates were determined using a technique called 'ANSWERS' (Zhu et al. PLoS ONE: in press) and pointwise ordinary least squares linear regression (PLR). ANSWERS is a regression technique which accounts for the increasing variability with declining VF sensitivity. The study sample size was calculated for treatment effects of a 10%, 20% and 30% reduction in progression rate in latanoprost-treated eyes over a 12-month period for power=0.90 and two-sided P=0.05. Sample sizes for pilot studies (power=0.80 and P=0.10) were also calculated.
Results: For a modest treatment effect of 20% rate reduction, 888 patients are needed (Table). For a more clinically significant treatment effect of 30% rate reduction, 390 patients are needed for an observation period of 12 months. For a pilot study, treatment effect of 30% rate reduction, 230 patients are required.
Conclusions: A clinical trial, with a VF outcome and an observation period of only 12 months, for a neuroprotective agent in patients on IOP-lowering treatment for glaucoma is feasible.

	ANSWERS			PLR		
Rate reduction	Slope (UKGTS latanoprost arm): mean (sd)	Target slope with neuro-protective treatment	Sample size (per arm)	Slope (UKGTS latanoprost arm): mean (sd)	Target slope with neuro-protective treatment	Sample size (per arm)
10%	-2.47 (2.25)	-2.22 (2.25)	1703	-6.58 (6.37)	-5.93 (6.37)	2019
20%	-2.47 (2.25)	-1.98 (2.25)	444	-6.58 (6.37)	-5.27 (6.37)	497
30%	-2.47 (2.25)	-1.73 (2.25)	195	-6.58 (6.37)	-4.61 (6.37)	220

Sample size required to identify a progression rate reduction of 10%, 20% and 30% in latanoprost-treated eyes
Commercial Relationships: David F. Garway-Heath, Alcon (C), Alcon (R), Alimera (C), Allergan (C), Allergan (F), Allergan (R), Bausch & Lomb (C), Bausch & Lomb (R), Carl Zeiss Meditec (F), Forsight (C), Heidelberg Engineering (F), OptoVue (F), Pfizer (F), Quark (C), Sensimed (C), Teva Pharmaceutica (C); **Haogang Zhu**, None; **David P. Crabb**, Allergan (F), Allergan (R), Merck (F), Merck (R), Pfizer (F)
Support: Pfizer Inc. (IIR 2005-1046); NIHR (HTA 11-129-24)
Clinical Trial: ISRCTN96423140

Program Number: 3551
Presentation Time: 5:00 PM–5:15 PM
The Relationship between Intraocular Pressure and Rates of Estimated Retinal Ganglion Cell Loss in Glaucoma.
Amir Marvasti[1, 2], Andrew J. Tatham[1], Linda M. Zangwill[1], Robert N. Weinreb[1], Felipe A. Medeiros[1]. [1]Hamilton Glaucoma Center, Department of Ophthalmology, University of California, San Diego, San Diego, CA; [2]Boston University School of Medicine, Boston, MA.
Purpose: To evaluate the influence of mean intraocular pressure (IOP) during follow up on rates of estimated retinal ganglion cell (RGC) loss in glaucoma.
Methods: 270 eyes of 178 subjects with glaucoma and suspected glaucoma were followed for mean ± SD of 6.3 ± 2.7 (range: 2.1 to 11.0) years, with an average of 9 ± 3 (range: 5 to 17) visits duri
Results: At baseline, the average SAP mean deviation (MD) was -2.4 ± 3.8 dB and average estimated RGC count was 776,077 ± 230,127 cells. Mean IOP during follow up was 16.8 ± 4.4 mmHg (range: 4.8 to 27.6). Average CCT was 554.1 ± 36.7 µm. There was a significant nonlinear relationship between the estimated rate of RGC loss and mean IOP during follow up with higher IOP associated with a higher rate of RGC loss. In a multivariable model including mean IOP, (mean IOP)^2, CCT, an interaction term CCT*mean IOP, and age at baseline, all variables were significantly associated with rate of RGC loss (P<0.05). Eyes with a mean IOP of 10 mmHg during follow up had estimated RGC losses close to the expected age-related loss of 6,944 cells per year. In contrast, mean IOPs of 16 mmHg, 22 mmHg, and 28 mmHg were associated with losses of 9,869 cells, 17,794 cells, and 30,718 cells per year, respectively (Figure 1).
Conclusions: Higher mean IOP during follow up is associated with greater rates of estimated RGC loss in eyes with glaucoma or suspected glaucoma.



Modeled relationship between estimated rate of RGC loss and mean IOP during follow up.
Commercial Relationships: Amir Marvasti, None; **Andrew J. Tatham**, Heidelberg Engineering (F); **Linda M. Zangwill**, Carl Zeiss Meditec Inc. (F), Heidelberg Engineering GmbH (F), Nidek Inc. (F), Optovue Inc. (F), Topcon Medical Systems Inc. (F); **Robert N. Weinreb**, Aerie (F), Alcon (C), Allergan (C), Bausch&Lomb

(C), Carl Zeiss Meditec (C), Carl Zeiss Meditec (F), Genentech (F), Heidelberg Engineering GmbH (F), National Eye Institute (F), Nidek (F), Novartis (F), Optovue (F), Sensimed (C), Topcon (C), Topcon (F); **Felipe A. Medeiros**, Alcon Laboratories Inc. (F), Alcon Laboratories Inc. (R), Allergan Inc. (C), Allergan Inc. (F), Allergan Inc. (R), Bausch & Lomb (F), Carl Zeiss Meditec Inc. (F), Carl Zeiss Meditec Inc. (R), Carl-Zeiss Meditec Inc. (C), Heidelberg Engineering Inc. (F), Merck Inc. (F), Method for estimating retinal ganglion cell loss using structure and function. (P), National Eye Institute (F), Novartis (C), Reichert Inc. (F), Reichert Inc. (R), Sensimed (F), Topcon Inc. (F)
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Clinical Trial: NCT00221897

Program Number: 3552
Presentation Time: 5:15 PM–5:30 PM

Evaluation of the Retinal Hemodynamics in Patients with Primary Open Angle Glaucoma and Differing Nocturnal Blood Pressure Profiles

Firdaus Yusof[1, 2], Richard Cheng[3], Nadia Espahbodi[3], Lee-Anne Khuu[3], Yvonne M. Buys[3], Graham E. Trope[3], Christopher Hudson[1, 3], John G. Flanagan[1, 3]. [1]School of Optometry and Vision Science, University of Waterloo, Waterloo, ON, Canada; [2]Department of Optometry and Visual Science, International Islamic University of Malaysia, Kuantan, Malaysia; [3]Department of Ophthalmology and Vision Sciences, University of Toronto, Toronto, ON, Canada.
Purpose: To evaluate the retinal hemodynamic response to normoxic hypercapnia among patients with primary open angle glaucoma (POAG) and differing nocturnal blood pressure (NBP) profiles, using Doppler spectral-domain optical coherence tomography (SD-OCT).
Methods: Doppler SD-OCT retinal blood flow (RBF) measurement was acquired using the circum-papillary double circular scan protocol of the RTVue system (Optovue Inc., Freemont, CA). The sample consisted of 17 healthy controls (group mean age 62±7 years; group mean NBP dip 14±8%); 17 POAG with normal NBP dip (age 66±9 years; NBP dip 11±5%), termed “dippers”; and 16 POAG with high NBP dip (age 64±7 years; NBP dip 24±5%), “over-dippers”. The NBP dip magnitude was calculated by taking the difference between mean arterial pressure (MAP) during the day and night while awake and asleep, respectively. Automated gas blender (RespiractTM, Thornhill Research Inc., Toronto) was used to stably provoke normoxic hypercapnia (15% increase in the end-tidal carbon dioxide partial pressure relative to homeostatic baseline). Six Doppler SD-OCT RBF scans were acquired, during baseline and also during normoxic hypercapnia. RBF parameters were calculated and ANOVA was used to compare values between groups ($p<0.05$).
Results: Total RBF at baseline was significantly different between the groups with controls being the highest (37.1±4.4μL/min), and over-dippers the lowest (29.6±9.0μL/min). Venous area showed significant differences at baseline between the groups with the lowest value in the over-dipper group, and the highest in the control group (39.9±7.0(x10-3)μm, and 46.6±6.6x(10-3)μm, respectively). Velocity was not significantly different between groups ($p=0.27$) at baseline. Breathing normoxic hypercapnia provoked an increase in flow that was significantly lower in the over-dipper group (1.0±8.6μL/min) and highest in the controls (8.2±10.8μL/min). Change in velocity was significantly different ($p=0.02$) between the groups, being highest in the control group (2.4±3.3mm/s) and lowest in the over-dipper group (-0.6±3.1mm/s). Venous area change was not significantly different between groups.
Conclusions: Patients with POAG who exhibited an exaggerated nocturnal reduction in MAP also demonstrated lower baseline RBF values and an impeded retinal vascular response to normoxic hypercapnia, indicating greater vascular dysregulation in this group.
Commercial Relationships: Firdaus Yusof, None; **Richard Cheng**, None; **Nadia Espahbodi**, None; **Lee-Anne Khuu**, None; **Yvonne M. Buys**, None; **Graham E. Trope**, None; **Christopher Hudson**, Optovue Inc. (F), Thornhill Research (I), Thornhill Research (P); **John G. Flanagan**, Carl Zeiss Meditec (C), Carl Zeiss Meditec (F), Carl Zeiss Meditec (R), Heidelberg Engineering (F), Heidelberg Engineering (R), Optovue Inc (F), Thornhill Research (I)
Support: Ontario Research Fund