ARVO 2017 Annual Meeting Abstracts

230 IOP Measurement and Characterization I
Monday, May 08, 2017 11:00 AM–12:45 PM
Room 301 Paper Session
Program #/Board # Range: 1596–1602
Organizing Section: Glaucoma

Program Number: 1596
Presentation Time: 11:00 AM–11:15 AM
Association between Glaucoma Progression and Intraocular Pressure Measurements Over Time
Bianca Nicolela Susanna1, Carolina Susanna2, Fabio B. Daga1, Alberto Diniz-Filho1, Linda M. Zangwill2, Robert N. Weinreb1, Felipe Medeiros1. 1Faculdade de Medicina do ABC (FMABC), São paulo, Brazil; 2Ophthalmology, UCSD, San Diego, CA.

Purpose: Intraocular pressure (IOP) is still considered the most important risk factor for the development and progression of glaucoma. Goldmann applanation tonometry (GAT) is the most widely used method of measuring IOP. However, it is well known that corneal properties affect the accuracy of this instrument. By measuring corneal biomechanical properties, the Ocular Response Analyzer corneal-compensated IOP (IOPcc) is proposed to be less dependent on corneal-induced artifacts when measuring the IOP. The purpose of this study was to determine the association between IOP measurements provided by GAT and ORA IOPcc and glaucoma progression over time.

Methods: This was a prospective observational cohort study including 213 eyes of 125 glaucoma patients followed for an average of 2.4 ± 0.6 years. At each visit, IOP measurements were obtained using GAT and ORA IOPcc. Glaucoma progression was defined based on a statistically significant slope from standard automated perimeter (SAP) mean deviation (MD) or spectral domain optical coherence tomography (SDOCT) Retinal Nerve Fiber Layer (RNFL) thickness change over time. Logistic regression models were used to investigate the relationship between mean IOP measurements and glaucoma progression over time, while adjusting for age and central corneal thickness (CCT).

Results: Mean baseline IOPcc and GAT IOP were respectively 15.8±4.9 and 14.2±4.8 mmHg. In univariable analyses, higher mean IOPcc measurements were associated with glaucoma progression (OR=1.08; 95% CI: 1.00 – 1.15; P=0.044). Although GAT IOP had similar odds ratio, the association with progression did not achieve statistical significance (OR = 1.04; 95% CI: 0.95 – 1.13; P=0.375). In multivariable analysis, higher mean IOPcc was also associated with glaucoma progression (OR=1.10; P=0.011).

Conclusions: ORA IOPcc measurements were significantly associated with structural and functional progression in glaucoma, indicating that they may provide valuable information when assessing the risk of disease progression.

Commercial Relationships: Bianca Nicolela Susanna, None; Carolina Susanna, None; Fabio B. Daga, None; Alberto Diniz-Filho, None; Linda M. Zangwill, Topcon, Inc (F), Optovue, Inc (F), Heidelberg Engineering, Inc (F), Carl Zeiss Meditec, Inc (F), National Eye Institute (F); Robert N. Weinreb, Optovue, Inc (F), Aeris Pharmaceutical (C), Heidelberg Engineering, Inc (F), Alcon Laboratories, Inc (C), Sensimed V (C), Topcon, Inc (F), Quark (F), Carl Zeiss Meditec, Inc (F), Allergan, Inc (C), Eyenovia (C), Bausch & Lomb (C), Genentech (F), Forsight Vision (C), Unity V (C); Felipe Medeiros, Allergan, Inc (R), Reichert, Inc (F), Sensimed (F), National Eye Institute (F), Allergan, Inc (C), Bausch & Lomb (F), Carl Zeiss Meditec, Inc (R), Novartis (C), Heidelberg Engineering, Inc (F), Reichert, Inc (R), nGoggle (I), Alcon Laboratories Inc (R), Topcon, Inc (F), Carl Zeiss Meditec, Inc (F), Alcon Laboratories, Inc (F), Merck, Inc (F), Carl-Zeiss Meditec, Inc (C)

Program Number: 1597
Presentation Time: 11:15 AM–11:30 AM
Goldmann applanation tonometer error relative to true intracameral intraocular pressure in vitro and in vivo
Sean J. McCafferty. Ophthalmology, University of Arizona, Tucson, AZ.

Purpose: Examine Goldmann applanation tonometer bias to intracameral intraocular pressure (IOP) in both human cadaver eyes and live human eyes. Also examine IOP bias changes due to patient position, and corneal biomechanical properties.

Methods: Twenty one (21) fresh human cadaver globes were manometrically modulated between 5 and 60 mmHg IOP measured by intracameral pressure transducer. IOP was measured with a Goldmann Applanation Tonometer (GAT) in both upright and supine positions. Central corneal thickness (CCT) was measured as an indication of corneal hydration. Additionally, eight (8) patients undergoing cataract surgery were manometrically adjusted to 20 mmHg IOP measured by intracameral pressure transducer. Prior to surgery, corneal resistance factor (CRF) was measured with an Ocular Response Analyzer (ORA) and CCT was measured. IOP was measured with a Perkins applanation tonometer in both supine and upright positions.

Results: The GAT tonometer measured IOP in cadaver eyes was 3.06+/−2.4 mmHg lower than intracameral transducer IOP in the upright position and 5.09+/−2.6 mmHg in the supine position (p<0.05). The Goldmann IOP measurement varied with corneal hydration as measured by CCT (747+/−66 microns) by 4.2 mmHg (correlation coeff.=0.23). The GAT IOP measured on live human eyes was 2.75+/−2.10 mmHg lower than intracameral transducer IOP in the upright position and 4.81+/−2.87 mmHg lower in the supine position. CCT in the surgical eyes (546+/−32 microns) indicated an IOP error correlation of 3.9 mmHg lower in thin corneas compared to thick corneas within the sample range (correlation coeff.=0.28). Likewise, CRF (9.1+/−2.1 tended toward a lower GAT measured IOP in corneas with a low CRF as compared to a high CRF by 4.0 mmHg within the sample range (correlation coeff.=0.18).

Conclusions: Goldmann IOP measures significantly lower than true intracameral IOP by about 3 mmHg in fresh cadaver eyes and this bias is confirmed in live human eyes. Supine position increases the IOP measurement bias to about 5 mmHg. Central corneal thickness (CCT) and corneal resistance factor (CRF) both appear to significantly affect the IOP measurement error by up to an additional 4 mmHg correlated over the ranges tested. These findings are useful in understanding the biomechanical effects creating both overall Goldmann IOP measurement bias and errors due to corneal biomechanical variability seen in patients.

Commercial Relationships: Sean J. McCafferty
Support: NIH R43 EY026821-01
Clinical Trial: NCT02910362

Program Number: 1598
Presentation Time: 11:30 AM–11:45 AM
Testing and Validation of a New IOP Telemetry Sensor Suitable for Implantation Directly into the Anterior Chamber
J Crawford C. Downs, Christopher A. Girkin, Brian C. Samuels. Ophthalmology, University of Alabama at Birmingham, Birmingham, AL.

Purpose: To test and validate a new piezoelectric pressure sensor implanted directly in the anterior chamber of nonhuman primates as a platform for IOP telemetry.

These abstracts are licensed under a Creative Commons Attribution-NonCommercial-No Derivatives 4.0 International License. Go to http://iovs.arvojournals.org/ to access the versions of record.
**Methods:** We have developed and validated an implantable telemetry system (Konigsberg Instruments; KI) that wirelessly records 500 IOP measurements per second continuously for up to 2-1/2 years (IOVS 52(10):7365-75). The KI system was based on a large, 6-mm-diameter pressure transducer that was screwed into a hole drilled into the orbital wall, and IOP was transmitted to the transducer via an aqueous-filled silicone tube inserted into the anterior chamber. The implant was large, and the battery required intrapitoneal placement. We have developed an updated bilateral IOP and ocular perfusion pressure (OPP) telemetry system based on the TSE Systems Stellar platform, that uses small 4-mm-long, 400-µm-diameter piezoelectric pressure transducers that can be implanted directly in the anterior chamber and carotid artery lumen (Figure). IOP was continuously recorded at 200 Hz for 15 seconds of every 150 second period in 4 eyes of 3 adult male rhesus macaques. The IOP sensors were calibrated via anterior chamber manometry every 2 weeks to assess signal drift, and physiologic IOP was evaluated for dynamic accuracy and sensitivity.

**Results:** Over the course of two months, IOP showed dynamic transients in response to systolic vascular filling, blinks, saccades, and corneal application tonometry with a Tonopen XL (Figure) that are consistent with measurements using our previous telemetry system. IOP transients from Tonopen application measured with the telemetry sensor matched those measured directly via anterior chamber cannulation with an external PowerLab pressure monitoring system. IOP transducer drift was 1-4 mmHg per month after heal-in, and the sensor was linear and accurate from 5-45 mmHg.

**Conclusions:** Results show that a new piezoelectric pressure transducer, small enough to be implanted in the anterior chamber of the human eye, is capable of accurately measuring mean IOP and IOP transients near-continuously over long periods, with low power requirements and signal drift. Such a sensor could be inductively powered, and may be translatable for human use via surgical implantation.

**Chloral hydrate sedation has a negligible impact on intraocular pressure (IOP) in infants and young children**

David S. Friedman1 2, Mohammed Karrayoui2 3, Varshini Varadaraj2, Karam Hamweyah1, Michelle Wilson3, Leyla Ali Aljasim1, Beatriz Munoz4, Megan E. Collins2.

1Ophthalmology, Johns Hopkins Wilmer Eye Inst, Dana Center, Baltimore, MD; 2International Relations and Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; 3Pediatrics, King Khaled Eye Specialists Hospital, Riyadh, Saudi Arabia; 4Ophthalmology, King Khaled Eye Specialists Hospital, Riyadh, Saudi Arabia.

**Purpose:** To determine the impact of chloral hydrate sedation on eye pressure in infants undergoing sedation for ophthalmic evaluation

**Methods:** Children aged 1 month to 5 years at King Khaled Eye Specialist Hospital undergoing examination under chloral hydrate induced sedation were enrolled in the study after written informed consent was obtained from their parents. Trained study personnel measured the IOP using an Icare tonometer prior to sedation (in some, not all children), at 25 minutes after sedation and then every 10 minutes until sedation was complete. Differences in means pre and first post sedation were compared using paired t-tests; IOP was monitored up to 2 hours post sedation, and its level was modeled using linear mixed models with time as the independent variable, allowing random effects for the intercept, the slope of time.

**Results:** A total of 115 children were enrolled, 50.4 % were female, and mean age was 2.1 (SD: 1.3) years from Jan 6th 2014 through June 16th 2016. Of the total, 86 (74.8%) participants had IOP measurement attempted prior to sedation, with 67 having pre-sedation IOP completed. Among those completing pre-sedation IOP, 48.8% were asleep or calm, and the rest (42.2%) were either slightly distressed or more distressed (IOP did not differ by level of agitation). Those with pre-sedation IOP available had similar demographics and health status (p > 0.05). Heart rate, respiratory rate and oxygen saturation all declined after sedation (p < 0.01). The mean dose of chloral hydrate administered was 81.1 (SD: 13.3) mg/kg, and sedation was deemed “adequate” in 96.3% after a single dose. Mean IOP among those with pre-sedation IOP was 19.7 (SD: 4.7) mmHg and this declined to 18.6 (SD: 4.8) mmHg at 25 minutes (p = 0.04). There was no trend towards further decline in IOP over time.

**Conclusions:** Chloral hydrate sedation is highly successful and low risk, and appears to alter IOP minimally in this prospective study of infants undergoing examination under anesthesia. Among those with pre-sedation IOP measurements, IOP decreased by an average of ≈1 mmHg. Those with higher IOP had similar stability of IOP under chloral hydrate sedation. Wider use of this form of anesthesia should be possible and effective in similar populations.

**Commercial Relationships:** David S. Friedman, None; Mohammed Karrayoui, None; Varshini Varadaraj, None; Karam Hamweyah, None; Michelle Wilson, None; Leyla Ali Aljasim, None; Beatriz Munoz, None; Megan E. Collins, None

**Support:** Internal Grant support from King Khaled Eye Specialists Hospital administered through Wilmer Eye institute

**Clinical Trial:** NCT02985567

These abstracts are licensed under a Creative Commons Attribution-NonCommercial-No Derivatives 4.0 International License. Go to http://iovs.arvojournals.org/ to access the versions of record.
Determining Neuronal Elements of IOP Regulation Using Mice

Alexander D. Kokini1,2, Krishnakumar Kizhatil1, Simon John1,2, The Jackson Laboratory, Bar Harbor, ME; 2The Howard Hughes Medical Institute, Chevy Chase, MD.

**Purpose:** The nervous system is important in controlling intraocular pressure (IOP), however the precise mechanisms of neural control need further evaluation. The mouse enables functional experiments and so we are characterizing limbal innervation in mice. To understand neuronal functions regulating IOP, we are using modern molecular techniques and fluorescent reporter mice to map limbal neurons and determine pressure dependent neuronal activity.

**Methods:** We used a whole-mount procedure of the anterior mouse eye to study the innervation of the entire limbus in 3D. The Prox1-GFP mouse strain was used to label Schlemm’s canal (SC). The Thy1-YFP strain was used to identify sensory neurons. Antibodies to detect sympathetic (tyrosine hydroxylase), parasympathetic (vesicular acetylcholine transporter, choline transporter), nitrergic (neuronal nitric oxide synthase), and axons (neurofilament) have been used. 3D limbal images generated using confocal microscopy and Imaris were used to map and identify the number and type of neurons and nerve termini in SC and trabecular meshwork (TM). Neuronal activity in response to pressure elevation was assessed using fluorescent neuronal activation sensors (GCaMP). To do this, eyes were cannulated and held at pressures of 13 and 33 mmHg for 30 minutes followed by fixation, immunolabeling and confocal microscopy.

**Results:** We have identified sympathetic nerve terminals and possibly non-nociceptive sensory terminals terminating in SC and TM. The TH labeled termini have varicosities and the YFP labeled termini appear as bouton like structures. Using GCaMP calcium sensor mice, we have identified neurons that are activated in the limbus in response to elevated pressure. These neurons are present in the SC and associated TM region.

**Conclusions:** We are constructing a detailed 3-dimensional (3D) map of the neuronal innervation of the AQH drainage structures to facilitate understanding of the neural control of IOP. Both SC and TM are highly innervated with activation of a subset of neurons in response to experimental elevation of IOP.

---

**Exoenzyme C3 transferase lowered IOP in rats**

Xuyang Liu1, Junkai Tan1, Yun Wang1, Ning Fan1, Paul L. Kaufman2, Ningli Wang3, 1Shenzhen Eye Hospital, Shenzhen, China; 2Department of Ophthalmology & Visual Science, University of Wisconsin-Madison, Madison, WI; 3Tongren Hospital, the Capital University of Medicine, Beijing, China.

**Purpose:** To evaluate the IOP-lowering effect of C3 exoenzyme (C3) using lentiviral vectors mediated C3 transduction in rat eyes.

**Methods:** Lentiviral vectors containing C3 (LV/C3) was prepared. Human trabecular meshwork (HTM) cells in culture were treated with LV/C3 at different MOI, and changes in cell morphology were observed. Five µL LV/C3 (8x10⁹ TU/ml) or eight µL LV (5x10⁹ TU/ml) were injected into the anterior chambers of the right and left eyes, respectively. The expression of GFP was visualized by Micron III Retinal Imaging Microscope and fluorescence microscope. IOP was measured every days post-injection for 8 days, and then every two days thereafter.

**Results:** LV mediated C3 expression induced changes in HTM cell morphology. The GFP expression in the regions of the anterior chamber angle was observed by frozen-section examination in 8th days after injection of LV/C3 or LV. In the LV/C3 group, IOP was significantly decreased in 3rd day post-administration when compared to control eyes or baseline, and this effect lasted for at least 40days (p < 0.05). No obvious inflammatory reactions were observed.

**Conclusions:** LV mediated C3 expression induced changes in cell morphology in cultured HTM cells, and lower the IOP when transduced into the anterior chamber of the rats.

**Commercial Relationships:** Xuyang Liu, None; Junkai Tan, None; Yun Wang, None; Ning Fan, None; Paul L. Kaufman, None; Ningli Wang, None
Program Number: 1602  
Presentation Time: 12:30 PM–12:45 PM  

**Stimulation of Hypothalamic Orexin Neurons using DREADD Technology Increases Intraocular Pressure**

Brian C. Samuels¹, Nathan Hammes², Chris Bernabe², Lauren Federici², Andrei Molosh³, Seema Bhatnagar⁴, Anantha Shekhar³, Philip Johnson². ¹Ophthalmology, University of Alabama at Birmingham, Birmingham, AL; ²Anatomy and Cellular Biology, Indiana University School of Medicine, Indianapolis, IN; ³Psychiatry, Indiana University School of Medicine, Indianapolis, IN; ⁴Anesthesiology and Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA.

**Purpose:** Orexins, a novel class of neuropeptides, play a key role in regulating circadian behaviors and autonomic functions. Previously, we showed that chemical stimulation of neurons in the dorsomedial/perifornical hypothalamus (DMH/PeF), the location of orexin neurons, evoked increases in intraocular pressure (IOP), intracranial pressure (ICP), and the translaminar pressure gradient. Pre-treatment with an orexin receptor antagonist attenuates the IOP and ICP response. Given that orexin neurons have extensive efferent projections to autonomic relays, we hypothesize that fluctuations in IOP are regulated, at least in part, by orexin neurons. To further test this hypothesis, we used chemogenetic DREADD technology (Designer Receptors Exclusively Activated by Designer Drugs) to stimulate DMH/PeF orexin neurons and examined the resulting IOP and cardiovascular effects.

**Methods:** Orexin neurons of Sprague-Dawley rats (n=9) were selectively transfected by microinjecting a DREADD adeno-associated virus (AAV) under the orexin promoter into the DMH/PeF region. One month was allowed for excitatory M3GqR DREADD receptor expression. Isoflurane anesthetized rats then received either clozapine-n-oxide (CNO; selective DREADD M3GqR agonist that is otherwise inert; 3mg/kg i.p.) or vehicle control in a crossover design. An iCareLab tonometer and a tail pressure cuff attached to a PowerLab system was used to record IOP and heart rate (HR), respectively. Group differences in IOP and HR response were evaluated by paired t-test (significance set at P<0.05). Immunohistochemistry was then performed to confirm selective transfection and activation of orexin neurons and downstream nuclei by c-fos analysis.

**Results:** Microinjection resulted in selective transduction and expression of M3GqR DREADD receptors onto ~80-90% of local orexin neurons. CNO caused a greater increase in IOP (4.1±2.4 vs 2.0±1.2 mmHg; p=0.02) and HR (96±29 vs 29±19 beats/min; p=0.001) compared to vehicle control. CNO injection caused a significant increase in c-fos+ orexin neurons in the DMH/PeF and other downstream targets of the orexin neurons compared to vehicle control.

**Conclusions:** These data further support the hypothesis that orexin neurons located in the DMH/PeF region play a role in mediating circadian fluctuations in IOP. Further, the orexin system may provide a novel target for future glaucoma therapies aimed at reducing circadian fluctuation of IOP.

**Commercial Relationships:** Brian C. Samuels, Indiana University Research & Technology Corporation (P); Nathan Hammes, None; Chris Bernabe, None; Lauren Federici, None; Andrei Molosh, None; Seema Bhatnagar, None; Anantha Shekhar, Indiana University Research & Technology Corporation (P); Philip Johnson, Indiana University Research & Technology Corporation (P)

**Support:** NIH Grants (K08EY023594, K01AG044466, & UL1TR001108), RPB, and Eyesight Foundation of Alabama