

ARVO 2020 Abstracts

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1. The development of novel electroretinogram stimuli to detect glaucoma using a handheld device

Abstract Number: 4043

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DisclosureBlock: Alan Kong, None; Luca Della Santina, None; Robert Stamper, None; Neeti Parikh, None; Taras Litvin, None; Emily Mak, None; Jennifer Currier, None; Hoover Chan, None; Yvonne Ou, None;

Purpose

Glaucoma is a progressive optic neuropathy that involves damage and subsequent death of retinal ganglion cells (RGCs). Functional assessment involves perimetry to quantify the degree of visual field loss, but this test is prone to subjectivity. Our laboratory has previously demonstrated that glaucoma results in the differential impairment of specific RGC types, with OFF-RGCs more vulnerable than ON-RGCs. Retinal function can be assessed with an electroretinogram (ERG), but standard ERG equipment is bulky and requires substantial testing time. In this study, we asked whether a handheld ERG recording device could be used in glaucoma patients to objectively detect relative changes to ON- and OFF-pathways.

Methods

Control and open-angle glaucoma subjects were recruited from UCSF glaucoma and comprehensive ophthalmology clinics. Patients with retinal diseases or significant cataracts were excluded. Data was recorded using the handheld ERG RETeval (LKC Technologies). We tested each eye with several standard electrophysiology paradigms set by the International Society for Clinical Electrophysiology of Vision (ISCEV). We also utilized a novel custom-written sinusoidal wave pattern of light in order to separate ON vs. OFF responses. The sinusoidal stimulus was modulated between 0.3 Hz and 50 Hz. Data was analyzed with a Wilcoxon rank-sum test.

Results

In total, 62 glaucoma eyes and 21 control eyes were tested. Baseline demographics were similar between the groups. The ERG results for the standard ISCEV protocols were largely similar to previous findings (e.g., PhNR amplitudes were depressed in glaucoma eyes). Our novel sinusoidal stimulus showed that for frequencies between 15 and 50 Hz, glaucoma eyes had significantly lower response amplitudes than control eyes. Most notably at 50 Hz, glaucoma eyes had a 48% reduction in ERG amplitude (control eyes: 3.50 ± 0.49 mV, glaucoma eyes: 1.82 ± 0.19 mV, $p = 0.0012$).

Conclusions

Our study is novel in that we utilized a sinusoidal light stimulus of varying frequencies. Studies in mice suggest that ERG responses to stimulus frequencies greater than 18 Hz reflect OFF pathway activity while 5 to 15 Hz reflect ON pathway activity. We found that the higher stimulus frequencies showed a greater decrease in response. A handheld ERG device using a sinusoidal wave pattern may provide an *objective, fast, portable, and more comfortable* diagnostic test to detect glaucoma.

2. Light adapted, full field, luminance response of patients with glaucoma using a handheld ERG device

Posterboard#: B0211

Abstract Number: 3868 - B0211

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DisclosureBlock: Germano Dalfito, None; Renata Moreto, None; Quentin Davis, LKC Technologies, Inc. Code E (Employment), Alex Teles Vasconcelos, None; Jayter Silva Paula, None; Andre Messias, None;

Purpose

To study retinal function in glaucoma using a light-adapted full-field ERG luminance-response series.

Methods

Nine patients (n=9 eyes) with primary open-angle glaucoma but preserved visual acuity and no other ocular disease were evaluated. Visual field test (Humphrey – Zeiss; SITA-Fast 24-2) and spectral-domain optical coherence tomography (Heidelberg) measuring peripapillary retinal nerve fiber layer thickness (RNFL) were performed. Full-field ERGs (RETeval, LKC) were measured using skin electrodes and fully dilated pupils with a short photopic hill protocol consisting of a 30 cd/m² background and a sequence of 8 flash stimuli logarithmically spaced from 0.1 to 22 cd.s/m². b-wave amplitude data as a function of flash strength were fit with a Gaussian to determine maximal b-wave amplitude (Vmax), flash strength at Vmax (x0), and width of the Gaussian component (w). Data were compared with 9 healthy subjects (control) in the same age range.

Results

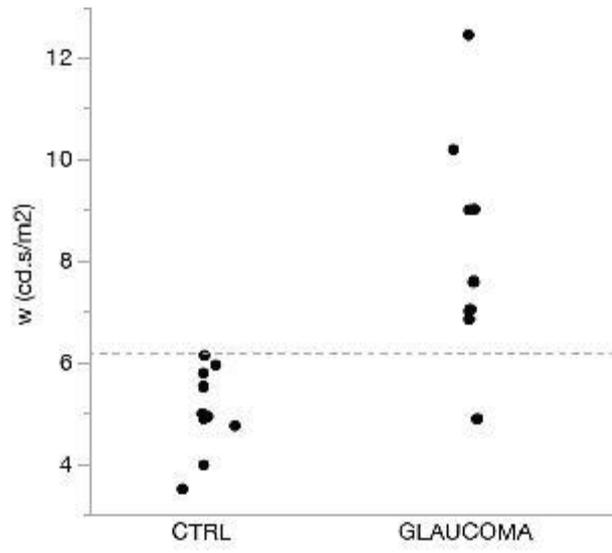
All subjects showed visual acuity of 20/20, visual field mean deviation was -5.5 ± 1.7 dB and RNFL thickness 93.5 ± 16.5 μ m. Comparing glaucoma subjects to controls (mean SEM), the following measurements did not show a statistically significant difference: dilated pupil diameter 6.6 ± 0.35 mm vs. 6.8 ± 0.3 mm (p=0.3), and x0 6.4 ± 0.9 cd.s/m² vs. 4.4 ± 0.8 cd.s/m² (p=0.1). In contrast, these measures did show differences: Vmax 22.5 ± 3.8 μ V vs. 36.2 ± 3.7 (p=0.02), and w 8.2 ± 0.5 cd.s/m² vs. 5.0 ± 0.5 cd.s/m² for controls (p=0.0006 - figure 1). No significant correlation was found between photopic hill parameters and pupil size, visual field MD, age or RNFL thickness.

Conclusions

Parameters derived from luminance-response series, which measure cone-driven function, show differences in subjects with early glaucoma. While our sample size is small, the width of the ERG photopic hill shows promise in the early detection of glaucoma.

Layman Abstract (optional): Provide a 50-200 word description of your work that non-scientists can understand. Describe the big picture and the implications of your findings, not the study itself and the associated details.

We reported changes in retinal function associated with primary open-angle glaucoma using a handheld device.



3. Predictive Value of ERG, OCT-A, and UWF-FA in Patients with Diabetic Retinopathy

Abstract Number: 4038

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Purpose

To assess the value of electroretinography (ERG), OCT-angiography (OCT-A), and ultra-wide field fluorescein angiography (UWF-FA) parameters to predict progression of diabetic retinopathy in eyes with moderate to severe non-proliferative diabetic retinopathy (NPDR).

Methods

In the TIME-2b trial 167 patients with NPDR were randomized to receive 48 weeks of treatment with AKB-9778 (a Tie2 activator) 15 mg once or twice daily, or placebo. Eligible eyes had ETDRS DR severity (DRSS) of 43, 47 or 53, BCVA of 20/30 or better, and no center-involved DME. Measurements at baseline included non-mydratric flicker ERGs (71 patients; RETeval device, DR Assessment protocol, Maa et al. 2016), OCT-A (74 patients), and OPTOS UWF-FA (101 patients). DRSS was graded on 7-field fundus photographs. Progression to DME was defined as an increase of central subfield thickness of $\geq 20\%$ or an adverse event of DME confirmed by the image reading center. PDR was defined as a DRSS of >53 , an AE involving neovascularization, or treatment for PDR. ROC analysis was used to assess predictive value of baseline measurements and pairs thereof.

Results

AKB-9778 did not have a statistically significant effect on DRSS or progression to DME/PDR, so data from all study arms were combined. 42 eyes progressed to DME/PDR; 21 of these eyes had ERGs, 17 had OCT-A, and 13 had UWF-FA. UWF-FA ischemia index, leakage index, and microaneurysm count were not predictive of progression. Statistically significant predictors (from worst to best, AUROC, 95% CI) include increased DRSS level (.60, .51–.69), decreased pupil response during ERG testing (.67, .55–.77), increased OCT-A FAZ area (.68, .52–.82), increased OCT-A total vessel length (.68, .56–.80), increased flicker implicit time (.73, .61–.83), and increased DR Assessment score (.79, .70–.87). The best pair was a logistic regression of the ERG-based DR Assessment score and OCT-A non-perfusion area (.86, .75–.94). When both tests were abnormal 73% (8/11) of eyes progressed. When both tests were normal 3.6% (1/28) of eyes progressed.

Conclusions

Prediction of progression of NPDR is important in the management of the disease. Pre-treatment ERG and OCT-A parameters were better predictors of progression to DME/PDR than DRSS or UWF-FA over 48-weeks of follow-up. The combination of functional and structural measures was better than either alone.

Layman Abstract (optional): Provide a 50-200 word description of your work that non-scientists can understand. Describe the big picture and the implications of your findings, not the study itself and the associated details.

4. Electrophysiological Assessment in Birdshot Chorioretinopathy: Use of a Portable Device in the Clinic

Posterboard#: B0280

Abstract Number: 5045 - B0280

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DisclosureBlock: Anna Michelle Waldie, None; Angharad E. Hobby, None; Isabelle Chow, None; Elisa Eleanor Cornish, None; Mathura Indusegaran, None; Alexandra Pekacka, None; Vuong Nguyen, None; Clare Fraser, None; Alison M. Binns, None; Miles R. Stanford, None; Christopher Hammond, None; Peter J. McCluskey, None; John R. Grigg, None; Omar Mahroo, None;

Purpose

Electrophysiological monitoring in Birdshot Chorioretinopathy (BCR) provides an objective assessment of disease activity, and the light-adapted 30 Hz flicker electroretinogram (ERG) has been shown to be sensitive to retinal dysfunction. This study explored use of a hand-held, full-field electroretinographic device (RETeval, LKC Technologies Inc., Gaithersburg, MD, USA) in BCR patients.

Methods

We analysed light-adapted full-field flicker ERG responses from 32 BCR patients. Recordings were obtained with the portable device using skin electrodes and parameters were compared with those obtained using standard recording techniques with conventional equipment. A random number generator was used to select right or left eyes from each patient for statistical analysis.

Results

Mean ERG amplitudes were $17.9 \pm 10.7 \mu\text{V}$ and $62.6 \pm 36.2 \mu\text{V}$ for the portable and conventional recordings respectively. The amplitudes recorded by the two systems were significantly positively correlated ($r=0.76$, $p<0.0001$, $n=32$; Pearson correlation coefficient). The mean peak time from the RETeval™ flicker ERG was $31.4 \pm 4.4 \text{ms}$, which was slightly shorter than the mean peak time from conventional ERGs, which was $32.9 \pm 7.1 \text{ms}$. The peak times were significantly positively correlated ($r = 0.53$, $p = 0.002$, $n=32$; Pearson correlation coefficient).

Conclusions

ERG results obtained by portable device correlated significantly with conventional ERG recordings. Our results suggest that portable recordings could potentially be used in the office setting to provide a rapid assessment of generalised cone system function in these patients, and might be applicable to other retinal diseases. Replication of these findings, and formal repeatability studies will be helpful.

Layman Abstract (optional): Provide a 50-200 word description of your work that non-scientists can understand. Describe the big picture and the implications of your findings, not the study itself and the associated details.

5. Electroretinography Using Nonsedated Handheld Electroretinogram through Closed Eyelids

Posterboard#: B0310

Abstract Number: 775 - B0310

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DisclosureBlock: Hussain Rao, None; Katie Keck, None; Scott Atkinson, None;

Purpose

To determine if readable electroretinography (ERG) responses can be obtained in normal adults through closed eyelids using a handheld device (RetEval). RetEval ERG system is a new device that allows ERG to be performed in awake patients using skin electrodes. However, it is unknown if readable ERG responses can be recorded through closed eyelids using this device.

Methods

Full field ERG using skin electrodes was used to record flicker and bright flash ERG responses in 40 eyes of 20 adult volunteers (age range 24-53 years). Stimulus intensity was increased to 30cd.s/m². Flicker ERG was obtained under photopic conditions while bright flash ERG was performed under scotopic conditions.

Results

Readable flicker amplitude and implicit time responses were obtained in all eyes. Readable bright flash amplitude and implicit time responses were obtained in 72.5% of eyes.

Conclusions

Readable and accurate electroretinography responses can be obtained through closed eyelids using a handheld device. Full field ERG responses elicited by increased stimulus intensity and measured with skin electrodes may be very useful in the following circumstances: 1) patients with opaque media 2) patients, such as children, who have difficulty maintaining open eyes for testing.

Layman Abstract (optional): Provide a 50-200 word description of your work that non-scientists can understand. Describe the big picture and the implications of your findings, not the study itself and the associated details.

An electroretinogram (ERG) is a commonly used test that measures electrical activity in the retina. The electrical activity that is measured by ERGs is secondary to light-induced flux of ions within the retina. The information obtained from an ERG can be used to diagnose a large variety of retinal pathology. Most commonly, contact lens electrodes are used as they are able to provide the most accurate and consistent readings. For certain patient populations such as children and intellectually impaired, it is difficult to achieve compliance with the placement of these contact lens. This increased difficulty frequently requires these patients to undergo the ERG under sedation. This study examines a novel mechanism for performing ERGs. This study was performed to determine if readable ERG responses can be obtained through closed eyelids using a handheld device (RetEval). The results of this study are applicable for those who have difficulty maintaining open eyes for testing and patients with an opaque media in their eyes.

6. How to Diagnose Optic Neuropathy in a Blink!

Posterboard#: B0362

Abstract Number: 3120 - B0362

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DisclosureBlock: Randy Kardon, None; Nitsan Duvdevan-Strier, None; Matthew J. Thurtell, None; Michael Wall, None; Melanie Truong, None; Cyrus Colah, None; Pieter Poolman, None;

Purpose

In response to a light stimulus, a reflex orbicularis contraction of the upper and lower eyelid occurs. Our purpose was to determine if the photic blink reflex can be used as an objective clinical measure of afferent visual pathology, in a similar manner to Relative Afferent Pupillary Defect (RAPD). We compared the orbicularis and pupillary responses to increasing light in subjects with and without unilateral optic neuropathy. We hypothesized that the orbicularis contraction correlates with pupil contraction for the same light stimulus and would produce a relative afferent eyelid defect (RAED) in optic neuropathy.

Methods

We conducted a case-control study to compare the eyelid response to light in normal eyes and optic neuropathy eyes. Eyelid and pupil responses to a 1 Hz, 5 seconds duration Ganzfeld light stimulus, increasing in intensity, were video recorded in each eye, using a hand-held ERG device (RETeval©, LKC Technologies, Gaithersburg, USA). Video frames were analyzed to assess percent change of palpebral fissure and pupil compared to pre-stimulus baseline. Inter-eye eyelid and pupil response asymmetry was quantified in 14 patients with unilateral optic neuropathy and 10 healthy subjects and compared to retinal nerve fiber and ganglion cell layer asymmetry.

Results

The eyelid response increased as a function of light intensity and was significantly decreased in the optic neuropathy eyes compared to the fellow, unaffected eyes ($P < 0.0001$), but not between the two eyes of the healthy subjects ($p = 0.547$). The eyelid response in optic neuropathy eyes correlated with the pupil response ($r = 0.66$, $P = 0.012$), ganglion cell layer ($r = 0.543$, $P = 0.0479$) and retinal nerve fiber layer thickness ($r = 0.622$, $P = 0.347$).

Conclusions

Patients with unilateral optic neuropathy display a relative afferent eyelid defect (RAED) in addition to RAPD. The eyelid response correlated with the pupil response and provides a novel, additional method for evaluating optic neuropathies, which could potentially be used even after pupil dilation.

Layman Abstract (optional): Provide a 50-200 word description of your work that non-scientists can understand. Describe the big picture and the implications of your findings, not the study itself and the associated details.

Objective neural reflexes in response to light entering the eye are useful as objective read-outs of the health of the eye. The pupil contraction to light has been used clinically for many years as a means for detecting input differences between the two eyes to detect and monitor treatment of retinal and optic nerve disorders. However, some patient's have iris damage that prevents the pupil from being used to detect light input to the retina and optic nerve to the brain. Some patients come to medical attention who have already had their pupils dilated with eye drops preventing this important neural reflex to light from being used. The eyelids also respond to light, which has been termed the photo-blink reflex. Even small just perceptible eyelid contractions can be assessed with video recording. We used infrared video recordings and image analysis of video frames to show that the eyelid narrowing in response to increasing light levels can be used to

objectively diagnose retinal and optic nerve problems that can be potentially blinding if not detected and treated early.

7. Chromatic Electroretinography in Non-Human Primates using a Novel Algorithm

Posterboard#: B0294

Abstract Number: 759 - B0294

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Purpose

To report the development and results of a novel chromatic electroretinography (ERG) algorithm using the RetEvet device (LKC Technologies) on healthy rhesus macaques (*Macaca mulatta*).

Methods

: An algorithm for chromatic ERG was developed. The general strategy to isolate the short, medium, and long wavelength cone responses was to maximally stimulate each cone cell subtype while suppressing the signal from the other two subtypes. For short wavelength cones, a blue flash on red background was used. Medium wavelength cones were detected by using a green flash on red background. For long wavelength cones, a red flash on blue background was used. Optimization of the suppressing effect of the background light was performed by selecting the background light intensity that maintains b-wave latency near the high-background limit while maximizing the b-wave amplitude. Chromatic ERG was performed on animals with normal eyes confirmed by anterior and posterior segment ophthalmic examination, fundus photography, spectral domain optical coherence tomography, fundus autofluorescence, and standard full-field scotopic and photopic ERG testing. Reported values, after excluding statistical outliers, are averages +/- standard error of the mean.

Results

The algorithm developed for relative isolation of the short, medium and long wavelength cone responses resulted in three unique waveforms. Chromatic ERG was performed on 14 normal animals. The short wavelength cones had an a-wave of -12.2 μV (+/-0.6 μV) at 14.59 ms (+/- 0.28 ms) and b-wave of 45.2 μV (+/-3.0 μV) at 27.1 ms (+/- 0.5 ms). The medium wavelength cones had an a-wave of -9.1 μV (+/- 0.7 μV) at 16.03 ms (+/- 0.26 ms) and b-wave of 37.7 μV (+/- 3.2 μV) at 27.42 ms (+/- 0.35 ms). The long wavelength cones had an a-wave of -9.8 μV (+/- 0.9 μV) at 15.80 ms (+/- 0.29 ms) and b-wave of 44.8 μV (+/- 3.1 μV) at 30.0 ms (+/- 0.6 ms). These cone subtype measurements were statistically significantly different in each parameter except b-wave amplitude ($P = 0.002, 0.02, 0.0003, 0.2$ for a-wave time, a-wave amplitude, b-wave time, b-wave amplitude, respectively).

Conclusions

Chromatic electroretinography can be performed successfully in non-human primates using a customized algorithm in conjunction with the RETevet device. Applications of this technique include investigation of color vision in non-human primates as well as response to gene therapy targeting cone photoreceptors.

Layman Abstract (optional): Provide a 50-200 word description of your work that non-scientists can understand. Describe the big picture and the implications of your findings,

8. Iris reflectance measurements in >1000 healthy adult twins: exploration of heritability and associations with eye color

Posterboard#: B0335

Abstract Number: 1866 - B0335

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DisclosureBlock: Andrea Kimberly Uy, None; Xiaofan Jiang, None; Alex Tanner, None; Mark Simcoe, None; Diana Kozareva, None; Katie Williams, None; Pirro G. Hysi, None; Christopher Hammond, None; Omar Abdul Rahman Mahroo, None;

Purpose

Eye color is highly heritable, and some ocular diseases can be associated with changes in levels of iris pigmentation. In this study, we explored iris reflectance measurements made with a portable device in adult twins, exploring intra-pair correlations and investigating whether these differed significantly between eye colors.

Methods

Healthy adult volunteers were recruited from the TwinsUK cohort. Participants underwent undilated photopic electroretinogram recordings using a portable electroretinography device (RETeval, LKC Technologies Inc., Gaithersburg, MD, USA) as part of a large electroretinography study. During recordings, the device captured a video image of the participant's eye. Iris pixel intensity (divided by that recorded from the pupil) was extracted from this image by the device's software. We quantified coefficients of intra-pair correlation for monozygotic (MZ) and dizygotic (DZ) twin pairs. Qualitative iris color was also noted (blue, grey, green, hazel, light brown or dark brown). Measurements were compared between iris color categories (one-way ANOVA).

Results

Recordings and images were obtained from 1626 participants. After exclusion of singletons, data was available from 1374 twins (454 MZ and 233 DZ pairs). 84% were female. Mean (SD) age was 53.6 (16.2) years for the whole cohort. Coefficients of intra-pair correlation were 0.75 and 0.44 for MZ and DZ pairs respectively. Mean measurements differed significantly ($p < 0.05$) between eye color categories for 10 out of 15 pair-wise comparisons (the following comparisons were not significant: blue-grey; blue-green; grey-green; green-hazel; hazel-light brown).

Conclusions

Iris reflectance ratio measurements, as quantified by the portable device, showed greater intra-pair correlation for MZ than DZ pairs, implying significant heritability. These measurements also differed significantly between eye color categories, suggesting possible utility as a continuous quantitative trait relating to iris pigmentation.

Layman Abstract (optional): Provide a 50-200 word description of your work that non-scientists can understand. Describe the big picture and the implications of your findings, not the study itself and the associated details.