iPhone-based Pupillometry: A Novel Approach for Assessing the Pupillary Light Reflex

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SIGNIFICANCE: The response of the pupil to a flash of light, the pupillary light reflex (PLR), is an important measure in optometry and in other fields of medicine that is typically evaluated by qualitative observation. Here we describe a simple, portable, iPhone-based pupillometer that quantifies the PLR in real time.

PURPOSES: The purposes of this study were to describe a novel application that records the PLR and to compare its technical capabilities with a laboratory-based infrared (IR) camera system.

METHODS: Pupil sizes were measured from 15 visually normal subjects (age, 19 to 65 years) using an IR camera system and the Sensitometer test. This test elicits pupillary constriction using the iPhone flash, records pupil size using the camera, and provides measurements in real time. Simultaneous recordings were obtained with the Sensitometer test and IR camera, and two measures were calculated: (1) dark-adapted steady-state pupil size and (2) minimum pupil size after the flash. The PLR was defined as the difference between these two measures. Pupil size was also recorded during the redilation phase after the flash. Bland-Altman analysis was used to assess the limits of agreement between the two methods.

RESULTS: Statistically significant correlations between the IR and Sensitometer test measures were found for the PLR ($r = 0.91$, $P < .001$) and redilation size ($r = 0.65$, $P = .03$). Bland-Altman analysis indicated a mean PLR difference of 6% between these two methods. The PLR limit of agreement was 14%, indicating that 95% of subjects are expected to have IR and Sensitometer test measurements that differ by 14% or less. Bland-Altman analysis indicated a mean redilation size difference of 1% between the two methods; the limit of agreement was 5%.

CONCLUSIONS: There is excellent agreement between pupil responses recorded using the Sensitometer test and IR camera. The Sensitometer test provides a highly promising approach for simple, portable, inexpensive pupillary measurements.

Optom Vis Sci 2018;95:953–958. doi:10.1097/OPX.0000000000001289

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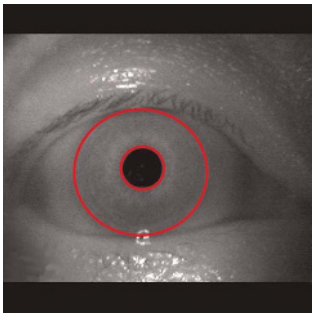

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The response of the pupil to a flash of light, the pupillary light reflex, allows for noninvasive, functional assessment of many neural and muscular structures. Recent studies have advanced our understanding of the pathways and mechanisms that underlie the pupillary light reflex, which has renewed interest in pupillometry as a tool for assessing retinal function in patients with acquired[1–7] and inherited[8–11] ocular dysfunction. In addition, pupillometry has been applied to study autonomic nervous system function in patients with a variety of conditions that are not typically considered ocular disorders including allergic rhinitis,[12] traumatic brain injury,[13] Alzheimer disease,[14,15] Parkinson disease,[16] and congenital central hypoventilation syndrome.[17] Traditionally, assessment of the pupil has been performed qualitatively by experienced clinicians using a penlight. More recently, infrared camera systems have been developed to provide quantitative measures of pupil size and reactivity, permitting assessment under both light- and dark-adapted conditions, as well as assessing pupil dynamics over time. Although existing infrared camera systems provide highly useful and precise measurements of the pupil, they are limited in that they are typically expensive, are not portable, and often require well-trained operators. Given these factors, pupillometry is generally performed only in large academic research centers.

Mobile smartphone applications have recently received substantial attention in medicine, as they overcome many of the aforementioned limitations. In fact, a smartphone-based infrared video pupillometer has been developed.[18] Although this smartphone-based pupillometer compared favorably with a commercially available device, the system required external infrared light-emitting diodes and custom post-processing of test data to derive pupil responses. Smartphone-based pupillometry has also been achieved using the built-in camera flash as a stimulus source and the camera to capture static images of the pupil.[19] This application, however, was limited in that only five images were obtained over a 6-second recording period, the pupil was not tracked, and size was not measured automatically. Rather, images of the pupil were saved, and these images were compared with a reference scale to estimate pupil size. Nevertheless, pupil size estimates obtained with the iPhone (Apple Inc., Cupertino, CA) camera images were similar to estimates made by a trained

observer using a penlight. In general, early studies have failed to provide simple, inexpensive, accurate, and portable real-time measures of pupil size and reactivity.

The present study describes a novel iPhone-based application, the Sensitometer test (KagenAir LLC, Appleton, WI), which elicits a pupil constriction using the iPhone camera flash and captures a video of the pupil during the constriction and redilation phases after the flash. The eye is tracked, pupil size is recorded over time, and the relative size of the pupil is calculated automatically. Pupil measurements obtained with this novel mobile technique were compared with those obtained simultaneously with a standard laboratory-based infrared pupillometer. The goal of the present study was to determine the extent to which the two techniques perform similarly as a first step toward developing an iPhone-based pupillometer that is suitable for clinical use.

METHODS

Subjects

Fifteen visually normal individuals (7 women, 8 men) volunteered to participate (mean [SD] age, 39.2 [14.0] years; range, 19 to 65 years). The subjects had no history of ophthalmic or neurological disease and had a best-corrected visual acuity of 0 logMAR (equivalent to 20/20 Snellen) or better. The study followed the tenets of the Declaration of Helsinki and was approved by a University of Illinois at Chicago institutional review board, and written informed consent was obtained from all subjects before testing.

Apparatus, Stimuli, and Procedure

A novel iPhone application (the Sensitometer test) was developed to generate the stimulus and record the pupil response. The stimulus consisted of two brief flashes of light produced by an iPhone 6S "rear-facing" camera flash. The initial flash was 3 seconds in duration, which elicited a large pupillary constriction. A second brief flash (a duration of 0.25 seconds) followed the offset of the first flash by 3 seconds. The second flash was used to illuminate the pupil, permitting pupil size to be measured as the pupil returned ("redilated") to baseline. The 3-second interval between flashes was selected to ensure that the pupil had sufficient time to begin redilation.

The rear-facing flash of the iPhone is produced by a light-emitting diode that has "cold white" characteristics. Fig. 1 shows the spectral emission of the light-emitting diode obtained with a spectroradiometer (PhotoResearch PR740; JADAK Inc., Syracuse, NY). The spectral emission predominately contains energy at short wavelengths (peak at 444 nm) and middle wavelengths (peak at 558 nm). The photopic illuminance was approximately 100 lux and in units of α-opic lux[20]: 74.7 (cyanopic), 60.3 (melanopic), 73.3 (rhodopic), 90.8 (chloropic), and 94.6 (erythropic). Thus, the light-emitting diode is expected to produce relatively low melanopsin activation, resulting in a pupil response that is primarily rod- and cone-driven.

After 2 minutes of dark adaptation, the iPhone was positioned vertically between the subject's eyes at a distance of approximately 10 to 12 cm, and the subject was instructed to keep his/her eyes open and steady and to minimize eye blinks. A test distance of 10 to 12 cm ensured that both pupils would be captured in the video frames and that the pupils would appear large enough to permit

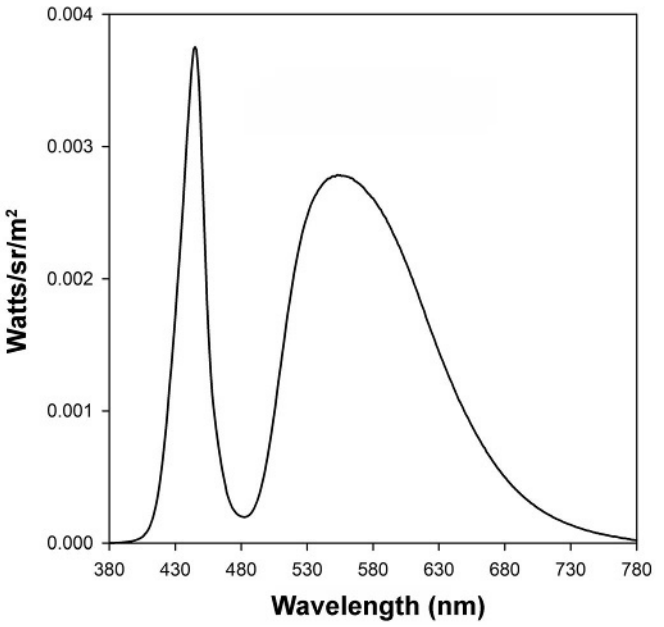

FIGURE 1. Spectral emission characteristics of the rear-facing iPhone camera flash.

analysis. After an audio cue produced by the application, the flash was delivered, and both pupils were digitally recorded simultaneously using the rear-facing iPhone camera. In the event of a blink during the first flash, the trial was discarded, and the test was repeated.

The Sensitometer test software uses the iPhone camera to capture a high-speed video (1920 × 1080 resolution at 120 frames/s) of the subject's pupils during the flash. Subsequently, the software fits ellipses to the inner (pupillary) and outer (limbus) margins of the iris for each video frame. The size of the pupil was defined in pixels for each video frame as the ratio of pupil diameter to iris diameter, a definition that has been used previously.[2,3,7,21,22] The pupil-to-limbus ratio eliminates the effect of test distance, as both the pupil and limbus sizes in the frame increase (or decrease) proportionally if the camera is moved toward (or away from) the subject. To minimize the effects of frame-to-frame noise, an exponential function was fit to the pupil size for each frame during the flash, and the pupil size was defined by the function. Of note, there is a delay of approximately 200 milliseconds between the onset of the flash and the initial pupil constriction (i.e., response latency)[23]; this delay permits an estimate of the baseline pupil size in the dark (median pupil size over a 150-millisecond window before pupil constriction). The application defines the maximal pupil constriction as the difference between this baseline pupil size and the maximal constriction determined by the exponential fit.

In addition to recording pupil size using the application, pupil size was simultaneously measured using a standard laboratory-based infrared camera system (ViewPoint EyeTrack System; Arrington Research, Scottsdale, AZ). This system allows for real-time binocular pupillometry with high spatial resolution (<0.03 mm) at a 60-Hz sampling rate. The eye-tracking system consists of a spectacle-mounted infrared camera that does not obstruct the field of view. The infrared camera–derived pupil data were analyzed offline using custom scripts programmed in MATLAB (MathWorks Inc., Natick, MA), which allowed for semiautomated

analysis as follows: first, a median filter with a 300-millisecond time window was applied to remove eye blinks. Next, pupil size for each video frame was defined in pixels as the ratio of pupil diameter to iris diameter, consistent with the definition used by the Sensitometer test software. The infrared camera is capable of imaging the pupil in the dark, which permitted the baseline pupil size (a 150-millisecond window before the stimulus onset) to be accurately determined. The maximal pupil constriction was defined as the difference between the baseline pupil size and the maximal constriction after the camera flash. Although pupil size was measured simultaneously using both techniques, the infrared camera system was not time locked to the flash produced by the iPhone. Consequently, the latency of pupillary constriction cannot be determined with the infrared camera system.

RESULTS

Both the Sensitometer test and the infrared camera captured pupil responses from both eyes simultaneously. As expected, the maximal pupil constrictions obtained from the left and right eyes were highly correlated, with an r value of greater than 0.95 and a P value of less than .001. In addition, the mean maximal pupil constriction of the 15 subjects obtained from the left and right eyes did not differ significantly for either method of measurement (both, $t < 2.02$; $P > .07$). Therefore, data from the two eyes were averaged for further analysis.

Fig. 2 shows the mean pupil size of the subjects over a 6.5-second window obtained with the Sensitometer test (black trace) and the infrared camera (red trace). The blue boxes along the abscissa indicate the time of the flashes. As noted previously, the infrared trace was not time locked to the flash; in Fig. 2, the infrared trace was shifted to best match the Sensitometer test trace. In addition, pupil size data are not available from the Sensitometer test between 3 and 6 seconds, as it cannot record pupil size in the dark. Despite differences in methodology, the two pupil traces were highly similar: the rates of pupil constriction, asymptotic values reached (maximal constriction), and size of the pupil during redilation were nearly equivalent. The pupillometry traces shown in Fig. 2 are intended to illustrate the general pattern of pupillary constriction obtained using each method over time; pupil responses for all 15 subjects are examined quantitatively hereinafter.

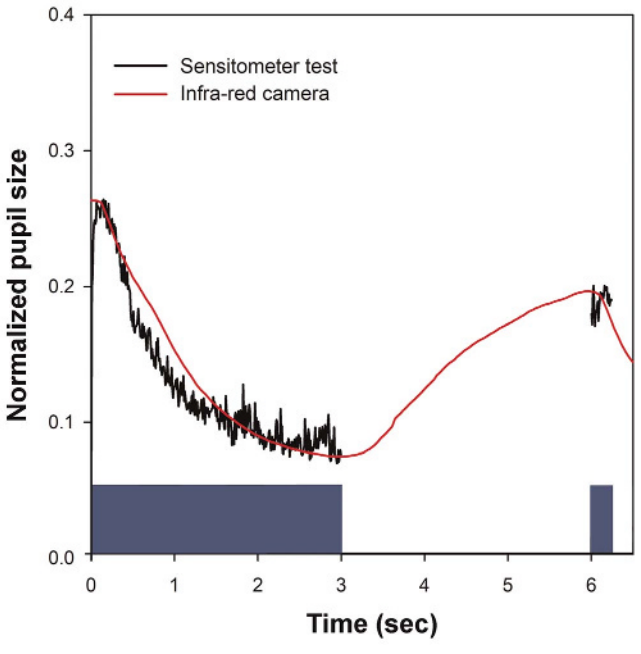

FIGURE 2. Mean pupil size of the 15 subjects measured over time using the Sensitometer test (black) and infrared camera (red). The blue boxes mark the onset and offset of the camera flash.

Fig. 3 (top) plots the maximal pupil constriction obtained with the infrared camera as a function of the maximal pupil constriction obtained with the Sensitometer test. The line is a linear regression fit to the data. There was a statistically significant correlation between the two measures ($r = 0.91$, $P < .001$). There was also a statistically significant correlation between the subjects' ages and the maximal pupil constrictions measured with the Sensitometer test ($r = –0.65$, $P = .009$) and the infrared camera ($r = –0.73$, $P = .002$). The lower panel in Fig. 3 shows results of a Bland-Altman analysis.[24,25] The difference between the two maximal constriction measurement techniques is plotted as a function of the mean of the two measures. The overall mean maximal pupil constriction difference between the two measures averaged across subjects was 6.0%. To determine if the maximal pupil constriction difference between methods varied as a function of the overall mean maximal pupil constriction, the data in Fig. 3 (lower panel) were fit by linear regression. The slope of the best-fit regression line fit to the maximal pupil constriction difference versus mean maximal pupil constriction data was not significantly different from zero ($t = –0.72$, $P = .48$). The nonsignificant slope indicates that the maximal pupil constriction difference between the two methods did not vary as a function of the mean maximal pupil constriction (i.e., subjects who had small pupil responses were not more or less variable than subjects with large pupil responses). Thus, a straight line with a slope of zero and a y intercept of 0.06 was fit to the data, represented by the dashed horizontal line. The limits of agreement between the two methods were then examined using the approach of Bland and Altman.[24,25] In this analysis, the value of each data point in Fig. 3 (bottom) was subtracted from the overall mean maximal pupil constriction value pooled across subjects (0.22). The result of this computation is equivalent to calculating the residuals from the dashed line. A linear regression line was then fit to the absolute value of these residuals. Following Bland and Altman,[24,25] the 95% limits of repeatability are given by

$$D \pm 1.96\sqrt{\pi/2 \times R}, \quad (1)$$

where D is the difference in maximal pupil constriction between the two methods and $R = b_0 + b_1 A$. The constants b_0 and b_1 are the y intercept and slope from the linear regression line fit to the absolute value of the residuals versus mean maximal pupil constriction, and A is the mean maximal constriction value for the infrared and Sensitometer test measurements for a given subject. The 95% limits of repeatability are shown as the solid gray lines in the lower panel of Fig. 3. These lines represent the limits within which 95% of the maximal constriction differences between methods are expected to fall. These data indicate that 95% of subjects are expected to have infrared and Sensitometer test measurements that differ by 14% or less. When the 6% mean difference

between methods was corrected by adding 6% to the Sensitometer test measurements, the limits of agreement improved to 9%.

Fig. 4 (top) plots pupil size during the second flash obtained with the infrared camera as a function of pupil size during the second flash obtained with the Sensitometer test. Data are presented only for the 11 subjects from whom second flash measures could be obtained; data from the other 4 subjects were contaminated by eye blinks. As in Fig. 3, the solid line is a linear regression fit to the data. There was a statistically significant correlation between the two measures ($r = 0.65$, $P = .03$). The lower panel shows the corresponding Bland-Altman analysis. The overall mean pupil size difference between the two measures averaged across subjects was 1%. The data in Fig. 4 (lower panel) were fit by linear regression; the slope of the best-fit regression line was found not to be significantly different from zero ($t = 1.32$, $P = .22$). This indicates that the pupil size during the redilation period after the flash was not dependent on the mean redilation pupil size. Thus, a straight line with a slope of zero and a y intercept of –0.01 was fit to the data (dashed

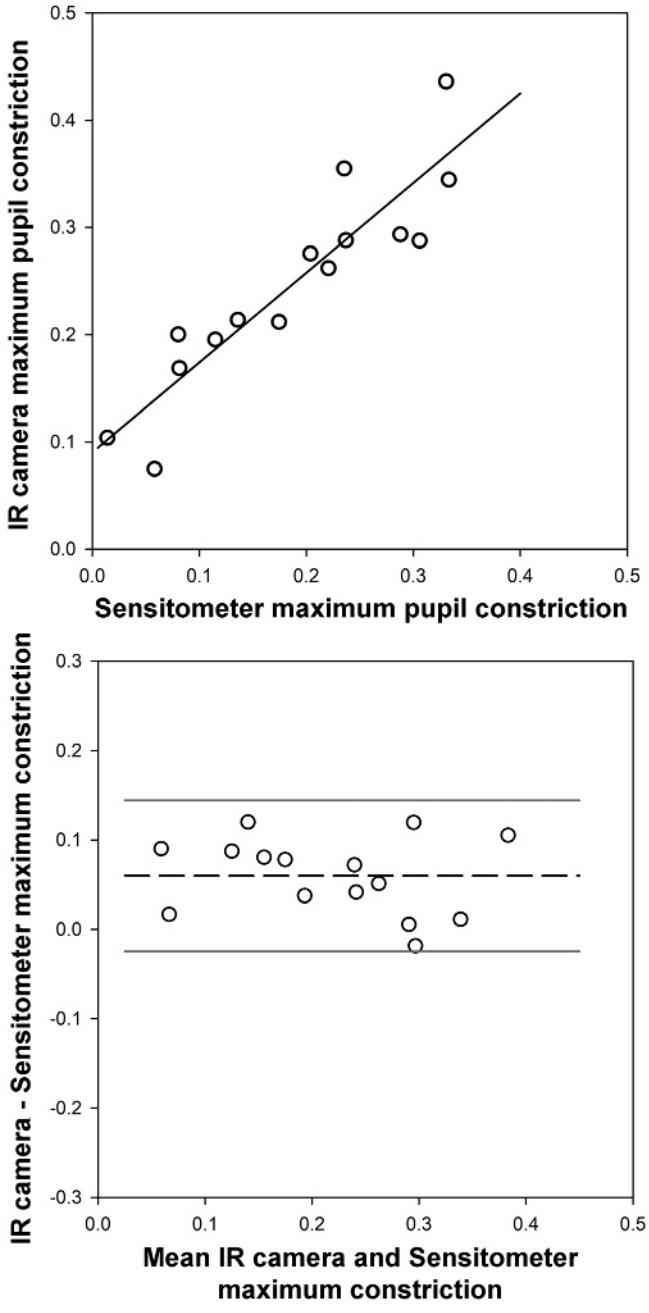

FIGURE 3. Maximal pupil constriction for each subject measured using the infrared (IR) camera is plotted as a function of the maximal pupil constriction measured with the Sensitometer test (top panel). The solid line is a linear regression fit, as described in the text. The bottom panel shows the results of the Bland-Altman analysis (see the test for details). The dashed line marks the mean difference between the IR camera and Sensitometer test measurements (6%), and the solid lines denote the 95% limits of agreement (14%).

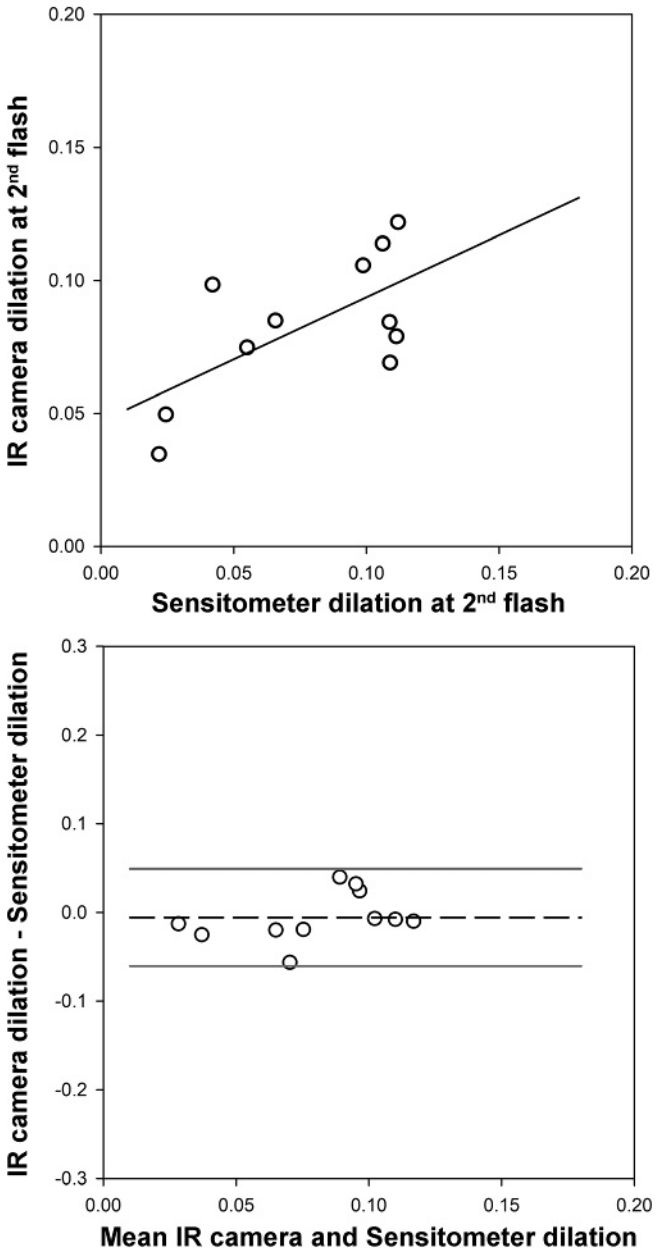

FIGURE 4. Pupil redilation size measured during the second flash. Conventions are as in Fig. 3.

horizontal line). The 95% limits of repeatability are shown as the solid gray lines in the lower panel of Fig. 4. These data indicate that 95% of subjects are expected to have infrared and Sensitometer test measurements that differ by 5% or less for the redilation measure.

DISCUSSION

The present study describes a novel iPhone-based pupillometry application: the Sensitometer test. In contrast to previous smartphone pupillometry applications, the present approach is completely software based, obviating the need for external optics or light-emitting diodes. In addition, pupil size is recorded over time with high temporal resolution, permitting pupil dynamics including maximal constriction, constriction velocity, and redilation size to be evaluated. Importantly, pupil sizes during both the constriction and redilation phases are calculated automatically and are provided to the user and/or clinician immediately after the test. Thus, the Sensitometer test holds great promise for use as an inexpensive, portable, simple-to-use pupillometry device. Previous reviews[26,27] have highlighted the utility of portable pupillometry systems in a variety of fields including surgery,[26,28] critical care, and anesthesiology.[26–30] In large part, the value of these instruments is in their ability to quantitatively evaluate a physiological response that has previously been assessed by qualitative observations.

The primary goal of the present study was to determine the extent to which measures of pupil size obtained with the Sensitometer test are similar to those obtained with laboratory-based infrared camera measurements. Our findings document high equivalence between these two techniques, with expected differences of less than 14% for maximal pupil constrictions generated by the camera flash. The Sensitometer test tended toward underestimating the maximal pupil constriction by approximately 6%, and correction of this error improved the limits of agreement to 9%. That is, the infrared camera and Sensitometer test measurements are expected to be within approximately 9% of each other. There was also high agreement for the pupil redilation measure after the flash, where the two measures can be expected to differ by approximately less than 5%. Note, however, that the redilation measure was contaminated by eye blinks in approximately 25% of the subjects, and responses from these subjects were excluded. Flash strength could be altered in future versions of the software to identify a more comfortable flash strength that may result in fewer eye movements and blinks while still permitting pupil tracking.

Future changes to the software could also include reporting the steady-state baseline pupil size before pupillary constriction. This could be of potential use in evaluating steady-state pupil size differences between the eyes to quantify anisocoria. Indeed, such a test could be performed in the dark or under room illumination. Constriction velocity is an additional metric that could be derived from the Sensitometer test measurements. However, pupil velocity and amplitude are highly correlated in visually normal subjects, such that subjects who have small pupil constrictions also have relatively slow constrictions.[31] Consequently, velocity and amplitude may provide somewhat redundant information, at least in visually normal subjects.

Although the agreement between the two pupillometry approaches was high, it is important to consider that all measurements in this study were obtained in a well-controlled laboratory environment. Further work is needed to determine how the Sensitometer test performs under nonlaboratory conditions in which ambient illumination cannot be as carefully controlled. An additional consideration is that the pupil latency could not be compared between the two methods. Future studies can be designed to time lock the iPhone flash to the infrared camera, permitting a direct comparison of temporal aspects of the maximal pupil constriction measured using the Sensitometer test and infrared camera. The focus of the present study was on visually normal individuals, and future studies are needed to determine if the Sensitometer test can identify individuals in the general population with ocular disease, traumatic brain injury, autonomic nervous system disorders, or disorders of smooth muscle reactivity.

In summary, there was excellent agreement between the novel iPhone-based Sensitometer test and the measurements made by infrared pupillometry. This novel technique offers a highly promising approach for simple, portable, and inexpensive pupil measurements for in-home or clinic use.

ARTICLE INFORMATION

Submitted: January 9, 2018

Accepted: June 10, 2018

Funding/Support: Foundation for the National Institutes of Health (P30EY01792); Research to Prevent Blindness (Dolly Green Scholar; to JJM); and National Eye Institute (R01EY026004; to JJM).

Conflict of Interest Disclosure: SLK owns KagenAir, which developed the iPhone-based pupillometer used in the present study. AG is an employee of KagenAir. BMS and JJM serve as consultants to KagenAir. The authors were responsible for the preparation of this manuscript and the decision to submit this article for publication. Each of the authors had full access to the study data and take full responsibility for their presentation in this article.

Author Contributions: Conceptualization: JJM, SLK; Data Curation: JJM, AG, SLK; Formal Analysis: JJM, BMS; Funding Acquisition: SLK; Investigation: JJM, BMS; Methodology: JJM, BMS, SLK; Project Administration: AG, SLK; Resources: SLK; Software: BMS, AG; Supervision: AG, SLK; Validation: BMS; Writing – Original Draft: JJM; Writing – Review & Editing: JJM, BMS, AG, SLK.

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